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Kinetic Studies Of The Thermolysis Of 3-Halogenated-4,5-Dihydro-3h-Pyrazoles

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KINETIC STUDIES OF THE THERMOLYSIS OF 3-HALOGENATED-4,5-DIHYDRO-3H-PYRAZOLES.

By

NEBIYOU DESALEGN YIFRU

Under the direction of G.Davon Kennedy and A.L. Baumstark

ABSTRACT

3-Chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3b**) and 3-bromo-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3c**) were prepared for the thermolysis project. The thermal decompositions of **3b** and **3c** were monitored using ^{1}H NMR spectroscopy. Plots of ln (% starting material) vs. time (sec) were linear for at least two half lives and the first order rate constants were determined over at least a 30° temperature range. The relative reactivity was found to be **3c** > **3b**. The activation parameters determined for the thermal decomposition of the pyrazoline at 150°C were found to be: for **3b** $\Delta H^{\ddagger} = 33 \pm 1.0$ kcal/mol, $\Delta S^{\ddagger} = -2.4 \pm 0.07$eu , $k_{150}{}^{0} = 7.34 \pm 0.44 \times 10^{-5}$ s^{-1} ; for **3c** $\Delta H^{\ddagger} = 30 \pm 0.2$ kcal/mol, $\Delta S^{\ddagger} = -6.9 \pm 0.03$ eu, $k_{150}{}^{o} = 42.3 \pm 0.7 \times 10^{-5}$ s^{-1}. Thermal decomposition of **3b** both neat and in dibromobenzene (DBB) resulted in the formation of an intermediate 2,3-diphenyl-4-methyl-1,3-pentadiene (**8**) as a major product and minor isomers of **8**. These intermediates then thermally decomposed to 1,1,3-trimethyl-2-phenyl-1H-indene (**9**) via an acid catalyzed process. In order to gain a mechanistic understanding (ionic vs. radical pathways) of the thermal decomposition of **3b**, a product study was conducted in protic solvents. In methanol and ethanol, **3b** underwent an ionic reaction (S_N1-type) with the solvent to produce 3-methoxy/ethoxy-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole

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LIST OF ABBREVIATIONS

DBB	1,3-dibromobenzene
3H-Pyrazole	4,5-dihydro-3-H-pyrazole
Ether	Diethyl ether
EDTA	Ethylene-diaminetetraacetate
IR	Infra red spectroscopy
LTA	Lead tetraacetate
MS	Mass spectroscopy
NMR	Nuclear magnetic resonance
NBS	N-BromoSuccinimide
PSI	Poly software International
TLC	Thin layer chromatography
THF	Tetrahydrofuran
TMS	Tetramethylsilane
Ts-F	P-toluenesulfonylfuloride
Ts-Cl	P-toluenesulfonylchloride
Ts-Br	P-toluenesulfonlybromide

CHAPTER I

Background

1.1 Pyrazoles and Pyrazole-Like Systems

Pyrazoles are five member heterocyclic compounds containing two adjacent nitrogen atoms and two double bonds (Figure 1). Pyrazole (1H-pyrazole, **2)** was first described by Knorr in 1883 (Knorr et *al.,* 1883) but prepared by Buchner in 1889 from decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**) (Buchner, 1889). The general numbering system for 1H-pyrazole is shown on Figure 2 (Jarboe et *al.,* 1967).

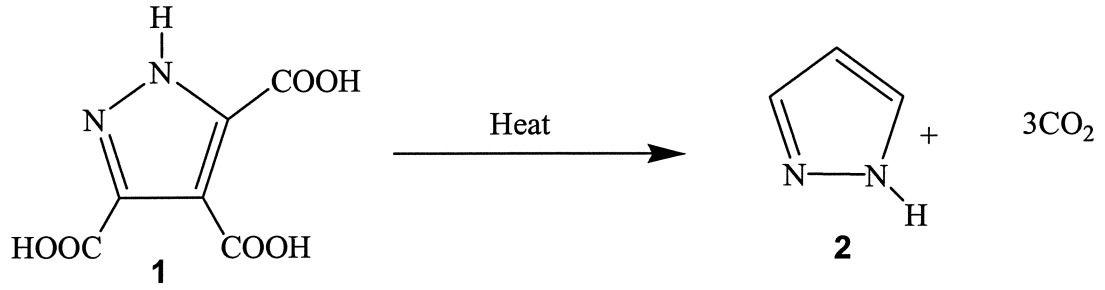
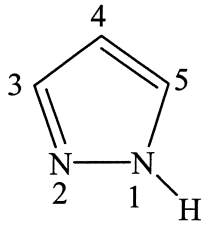


Figure1. The preparation of pyrazole by the decarboxylation of pyrazole-3,4,5-tricarboxylic acid (Buchner, 1889).



1*H*-Pyrazole

Figure 2. Numbering system for 1H-Pyrazole (Jarboe et *al.,* 1967).

1.2 Nomenclature of Pyrazoles and Related Systems

Pyrazoles and related ring systems can be designated as 1H, 2H, 3H and 4H-pyrazoles. The 2H and 3H-pyrazoles can be called as pyrazolines or dihydropyrazoles. The designation 1H, 2H, 3H, 4H prior to the word "pyrazole" shows the location of hydrogen atom which corresponds to the lowest numbering system for the nitrogen or the location for saturation (Figure 3). The word "dihydro" indicated the location of a formally reduced double bond. For dihydro 2H or 3H pyrazole, the compound must contain one double bond. In order to be named as 4H-pyrazole, which is also known as cyclic azine or isopyrazole, the compound must contain two double bonds and one tetrahedral carbon (Kevin et *al.,* 1984).

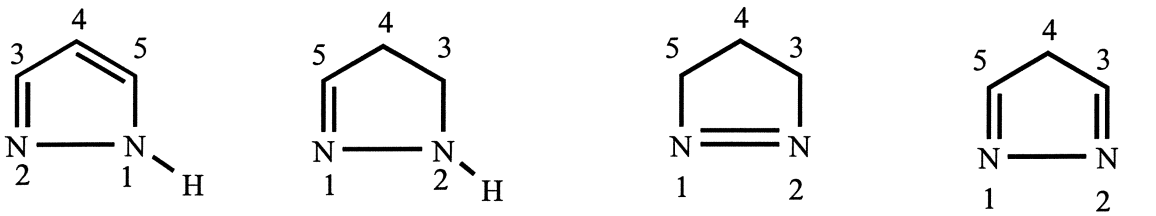


Figure 3. The naming system for pyrazoles and related systems.

1.3 Synthesis of Pyrazoles and Related Systems

There are several ways to synthesize pyrazoles and related systems. One of the classical synthetic methods is the 1,3-dipolar cycloaddition reaction. This reaction is analogous to the Diels-Alder reaction in that it occurs via concerted [4π+2π] type cycloadditions (Huisgen et *al.,* 1963(65); Padwa, 1984) and is stereospecific *syn* addition (Auwers et *al.,* 1929,1932; Auken et *al.,* 1962). Examples of 1,3-dipolar cycloaddtions are the reaction between diazomethane and olefinic double bonds activated by electron–withdrawing groups (McGreer et *al.,* 1965) and diazomethane additions to the diesters (Auwers et *al.,* 1929,1932; Auken et *al.,* 1962). However,

such reactions have been usually limited to the synthesis of tetra, tri or less substituted products (Figure 4).

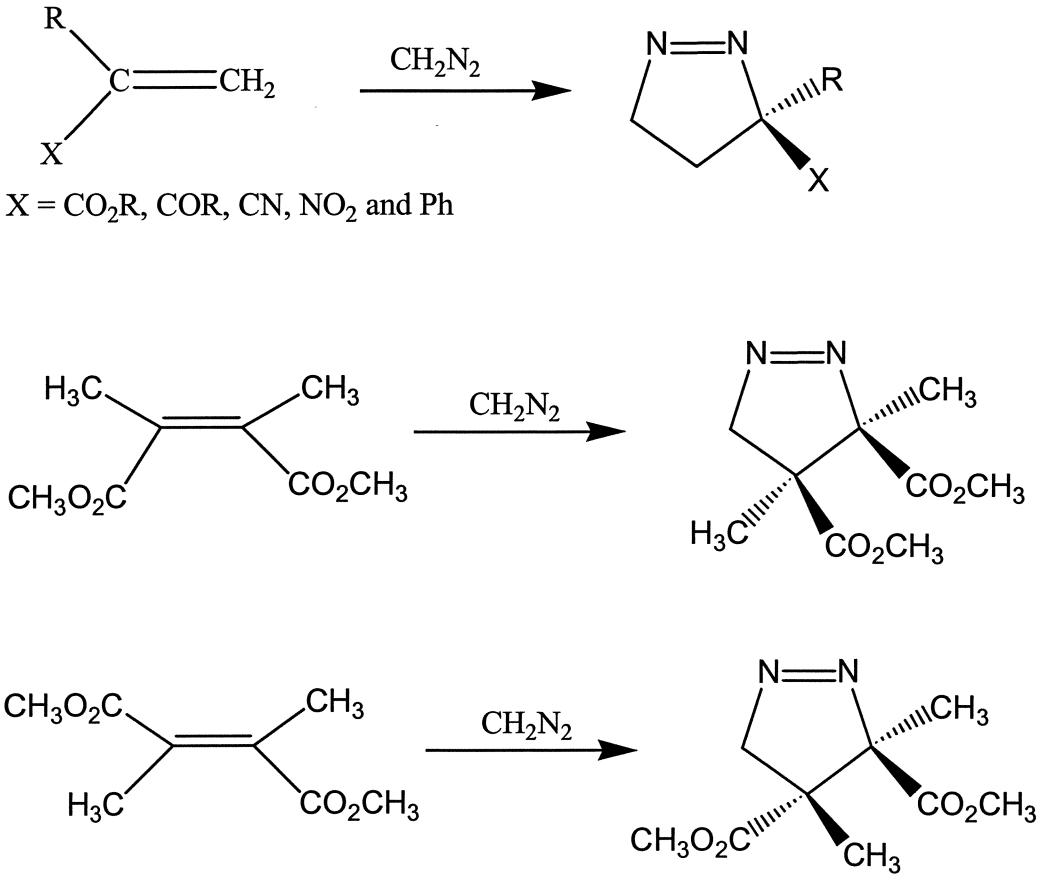


Figure 4. Addition of diazomethane to olefinic double bonds to make 4,5-dihydro-3H-pyrazoles (Auwers et *al.,* 1929,1932; Auken et *al.,* 1962, McGreer et *al.,* 1965).

The synthesis of pyrazolidine from 1,3-dibromopropane and hydrazine has been reported (Buhle et *al.,* 1943) and it provided an alternative route for the synthesis of dihydro 3H-pyrazoles (Figure 5). However, this reaction is limited to the synthesis of pyrazolines that do not have bulky substituents at C-3 and C-4 positions, due to need of an S_N2 reaction by hydrazine.

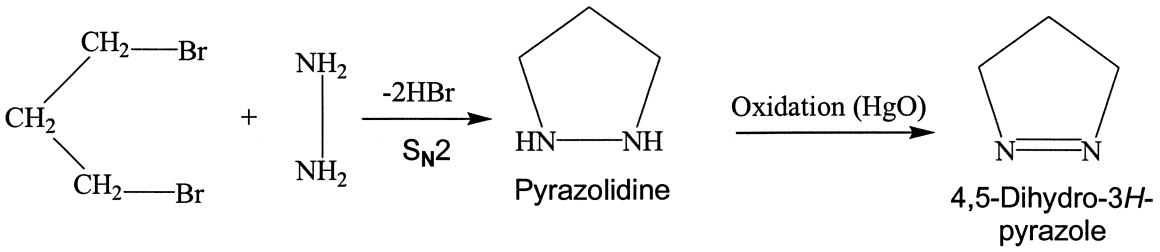


Figure 5. Pyrazolidine can serve as intermediate in the synthesis of dihydro-3H-pyrazoles (Buhle et *al.,* 1943).

Dihydro-2H-pyrazoles can be produced by subsequent cyclization of chalcones with hydrazine (Knorr,1893; Garge, et *al.,* 1971; Thakare, et *al.,* 1994; Ankhiwala, et *al.,* 1994). Chalcones (α,β-unsaturated ketones) are products of base-catalyzed aldol condensation reactions of aromatic ketones and aldehydes. The condensation of chalcones with hydrazine using microwave irradiation (MWI) instead of heat was reported (Azarifar et *al.,* 2003) as an efficient method in the synthesis of variety of 3,5-dihydro-1H-pyrazoles.

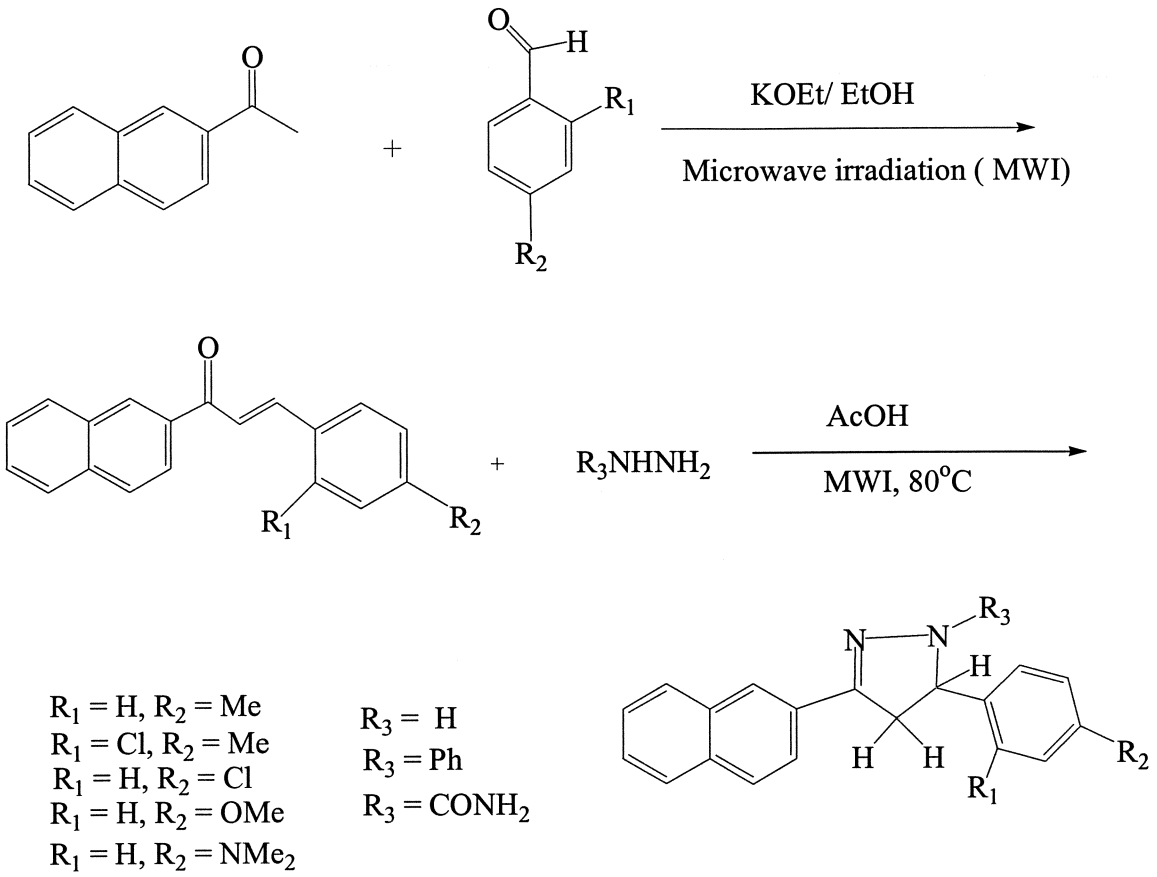


Figure 6. Efficient method for the synthesis of 3,5-arylated-dihydro-1H-pyrazoles under MWI heating system (Azarifar et *al.,* 2003).

An efficient way of making highly substituted pyrazoles is the condensation of 1,3-diketones with hydrazine (Baumstark, et *al.,* 1990). A good example of this would be the synthesis of 3,5-diphenyl-4H-pyrazole (**2**) from the condensation of hydrazine and 2,2-dimethyl-1,3-diphenyl-1,3-propanedione (**1**) (Figure 7).

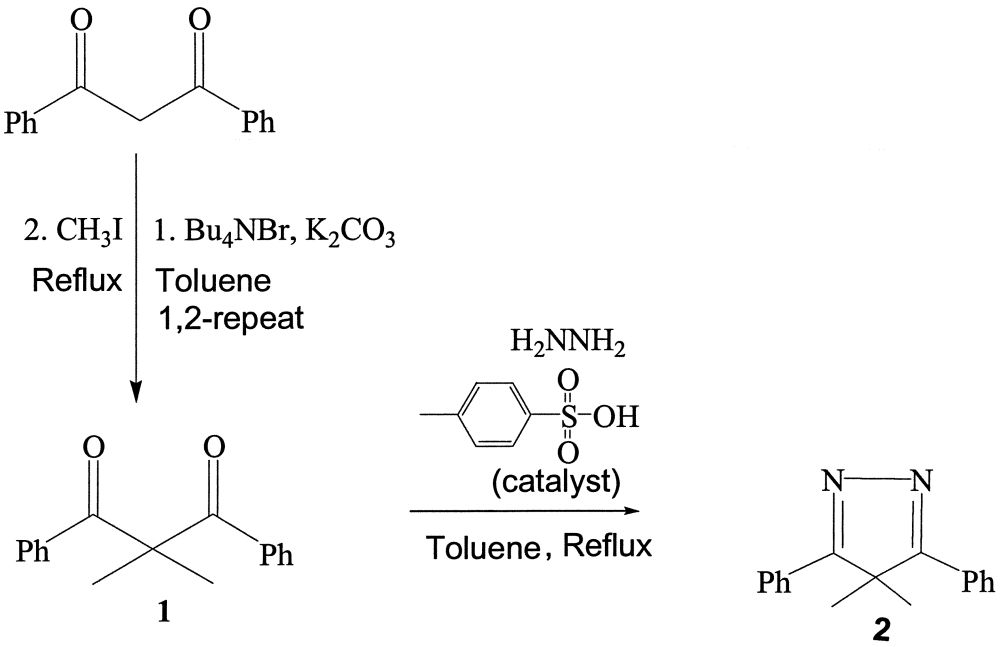


Figure 7. A convenient pathway for the preparation of 4,4-dimethyl-3,4-diphenyl-4H-pyrazole (**2**) (Baumstark et *al.,* 1990).

1.4 Uses of Pyrazo(le/line)

Pyrazo(le)/line and their derivatives are important biological agents. For example, some derivatives of pyrazoles exhibit anti-proliferative (Romero et *al.,* 2002) or anti-inflammatory (Rani et *al.,* 2004) properties. According to Rani et *al.*, (2004), compounds having chalcone, pyrazoline or azo moiety at position 3 of the indole nucleus do exhibit significant anti-inflammatory activities (Figure 8). Pyrazoline substituted at position 3 of the indole possess more anti-inflammatory activities than their corresponding chalcones. The diaryl-substituted pyrazole and the commercial drug that is known by the name celebrex(celecoxib) is another class of pyrazole that has anti-inflammatory, anti-pain, analgesic and antipyretic activities in animals (Drug profile of celebrex by Pfizer manufacturer) (Figure 9).

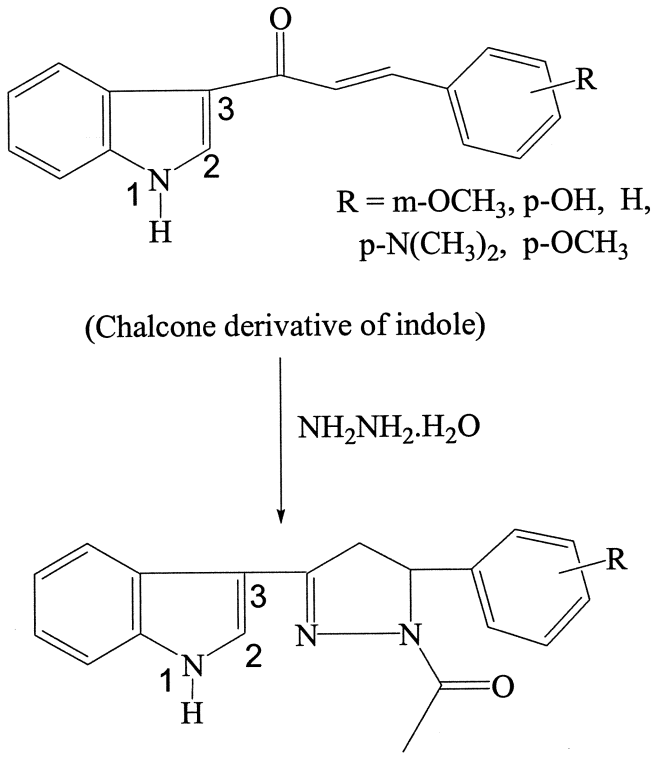


Figure 8. A pyrazoline derivative of indole reported to have superior anti-inflammatory activities (Rani et *al.*, 2004).

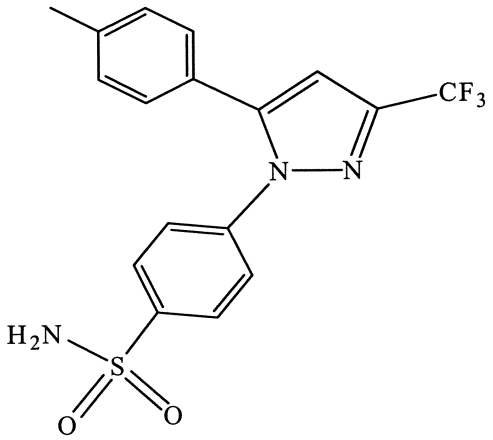
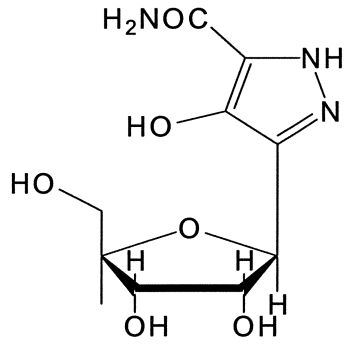
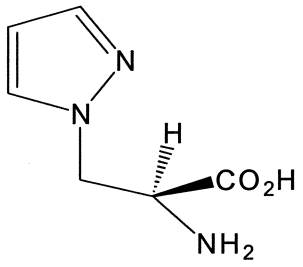


Figure 9. 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1ylbenzenesulfonamide, which has a commercial name "Celebrex", is anti-inflammatory and anti-pain drug.

Pyrazomycin and β-(1-pyrazolyl) alanine (Figure 10) are known for their antibiotic activities. β-(1-pyrazolyl) alanine is a natural product that contained pyrazole and was found in watermelon seeds (Noe et *al.,* 1959).



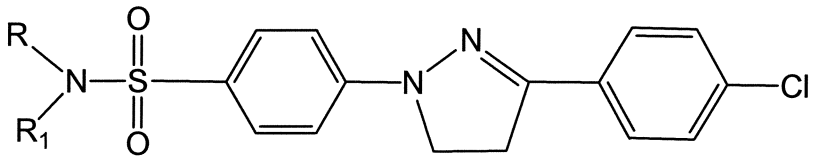
Pyrazomycin



β-(1-pyrazolyl) alanine

Figure 10. Pyrazomycin and β-(1-pyrazolyl) alanine are known for their antibiotic activities (Noe et *al.,* 1959).

In addition to pharmaceutical uses, pyrazo(les)/lines have several industrial applications. For example, 1-(4-Sulfamoylphenyl)-3-(4-chlorophenyl)–3,4-dihydro-2H-pyrazole (Figure 11) has been used to improve the brightness of fabrics (Bochenkova et *al.,* 1978) and phenyl pyrazole (Figure 12) is used as an optical and chemical bleaching agent (Geigy, 1963).



R = H, CH_2CH_2OH R = H

$R_1 = CH_2CH_2OH$ $R_1 = CH_2CH_2OSO_3Na$, $CH_2CH_2NEt_2$

Figure 11. 1-(4-Sulfamoylphenyl)-3-(4-chlorophenyl)-3,4-dihydro-2H-pyrazole is fluorescent whitener for synthetic fibers and wool (Bochenkova et *al.*, 1978)

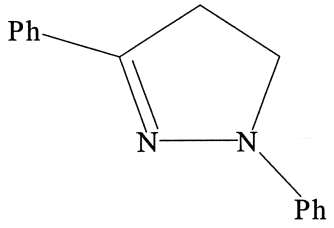


Figure 12. 1,3-diphenyl-4,5-dihydro-2H-pyrazole has been used as a bluing agent (Geigy, 1963).

Pyrazo(le)/lines also have a wide spectrum of synthetic applications. Historically, pyrazolines are known for their use in the synthesis of cyclopropane products upon thermolysis. For example, thermolysis of a series of methoxy and acetoxy hexasubstituted-4,5-dihydro-3H-pyrazoles (Vasquez et *al.*, 2000) provided hexasubstituted methoxy and acetoxycylopropane products respectively in high yields.

In the past, there have been no extensive studies in the thermolysis of a halogenated pyrazolines. In 1989, Yoshiko and co-workers reported that the thermal decomposition of chlorinated pyrazolines at lower temperature provided a mixture of cyclopropane and olefin products. According to Yoshiko (1989), the mechanism for the formation of olefin (**11Z**) is a concerted type (Figure 13) while cyclopropanes (**12Z/E,13Z/E**) were formed via a diradical intermediates (Figure 14).

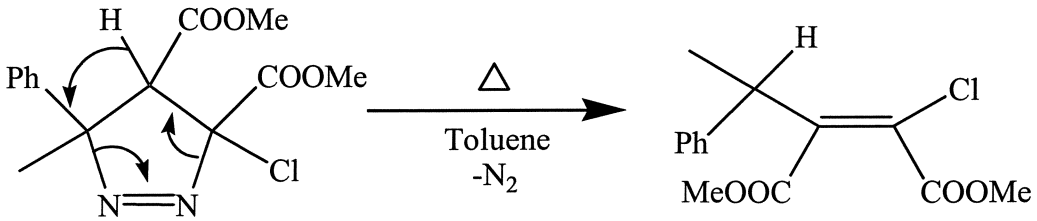
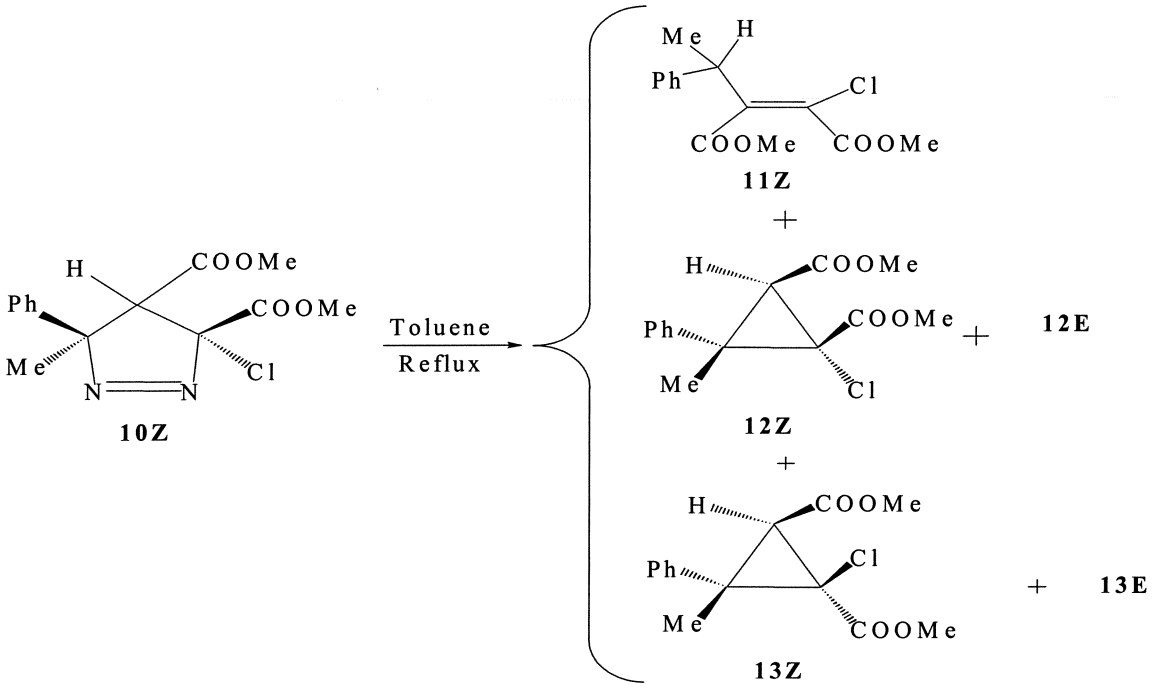


Figure 13. Mechanism in the formation of olefin minor product (**11Z**) upon thermolysis of pyrazoline (**10Z**) in refluxing toluene (Yoshiko et *al.*, 1989).



Lit. %

Yields (Yoshiko et *al.*, 1989):
11Z = 4%, **12Z** = 16%,
12E = 50%, **13Z** = 15%, **13E** = 6%

Figure 14. The thermolysis of halogenated pyrazoline (**10Z**) resulted in a mixture of olefin and cyclopropane products (Yoshiko et *al.*, 1989).

1.5 Research Objectives

Recently,trans-3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole(**3b**) (Kennedy,et *al.*, 2004) and trans-3-bromo-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3c**) have been synthesized by a new synthetic route in order to carry out the kinetic and product studies by thermal decomposition. To the best of our knowledge there have been no previous studies on the thermolysis of **3b-c**. The objectives of this research are:

1. To determine rate constants and activation parameters ($\Delta H^{\ddagger}$,$\Delta S^{\ddagger}$,$\Delta G^{\ddagger}$) for the thermolysis of **3b-c.**
2. To obtain mechanistic insights on the thermolysis of **3b** and **3c** by combining information gathered from both kinetic and product studies.
3. To determine if the thermolysis of **3b-c** is a new route to the synthesis of halogenated/hexasubstituted cyclopropanes.

CHAPTER II

RESULTS

2.1 Control Experiments

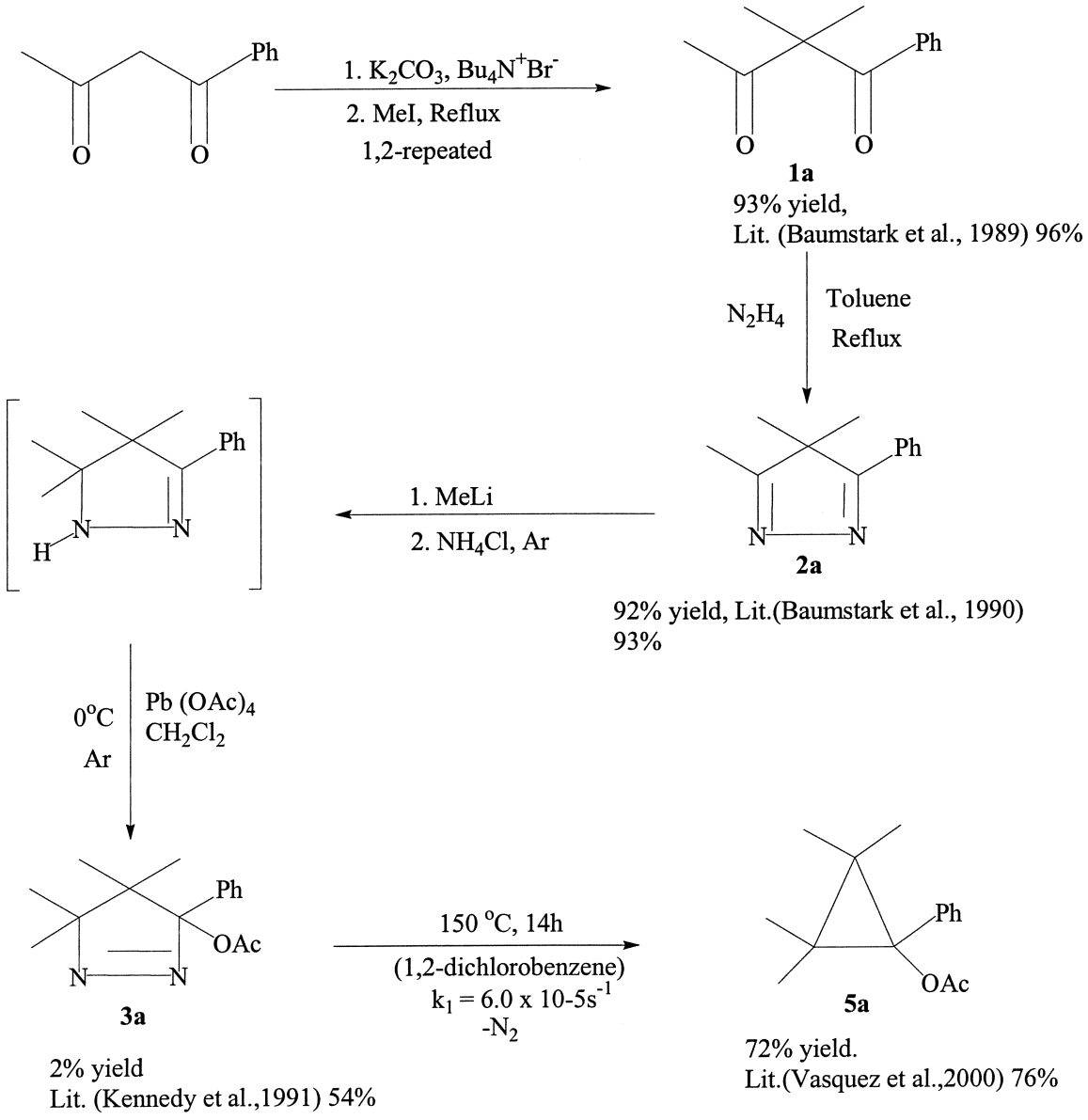


Figure 15. Overview of procedural steps in the preparation and thermolysis of **3a**.

The preparation of 3-acetoxy-4,4,5,5-tetramethyl-3-phenyl-4,5-dihydro-3H-pyrazole (**3a**) was carried out in a four-step process. The first two steps were the alkylation processes in which 1-benzoylacetone was dialkylated to produce 2,2-dimethyl-1-phenylbutane-1,3-dione (**1a**) in 93 % yield. The third step was the condensation reaction of **1a** and hydrazine that resulted in the formation of 3,4,4-trimethyl-5-phenyl-4H-pyrazole (**2a**) in 92% yield. The final step was the preparation of **3a** via an oxidation reaction of the intermediate formed by methyllithium addition to **2a** by $Pb(OAc)_4$. Failure to keep O_2 out of the $Pb(OAc)_4$ reaction resulted in the formation of **3a** in an extremely low yield. Since sufficient material was in hand to carry out the necessary studies, no attempt was made to repeat the literature procedure under N_2 to obtain a yield that is at least comparable to the literature value of 63%.

Once the purity of **3a** was verified by ^1H NMR, MP and MS data, the first order rate constant for the thermolysis of **3a** was determined at 150°C in 1,2-dichlorobenezene. The progress of the thermolysis process was observed by NMR methods. The disappearance of the most up-field methyl signal of the 3H-pyrazole derivative versus that of the methoxy group of the internal standard (2-bromoanisole (b.p=223°C)) was monitored. These two signals were integrated as a means to measure the concentration of the starting material as a function of time. The first order rate constant for the thermolysis of **3a** at 150°C was determined from the slope of ln[%starting material(SM)] versus time (sec) (Figure 16), which is $6.0\pm0.6 \times 10^{-5}\ s^{-1}$.

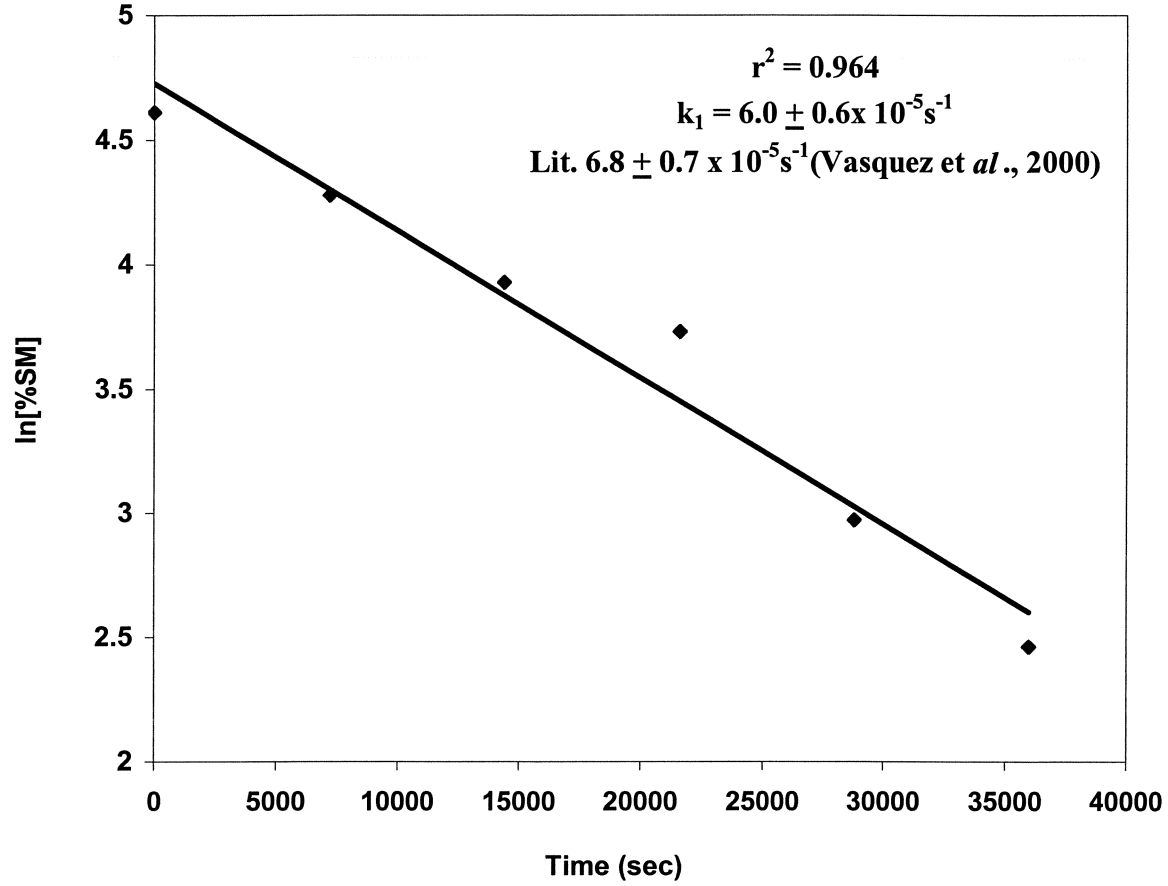


Figure 16. Plot of ln[%starting material] vs. time (sec) for the thermolysis of 3-acetoxy-4,4,5,5-tetramethyl-3-phenyl-3H-pyrazole (**3a**) in 1,2-dichlorobenzene at 150 °C.

The correlation coefficient (r) of the thermolysis of **3a** was 0.98 for at least two half lives. This indicates a good linear relationship between ln [% starting material] and time(sec). The only observable product from the thermolysis of **3a** at 150°C in 1,2-dichlorobenzene was 1-acetoxy-2,2,3,3-tetramethyl-1-phenyl cyclopropane (**5a**), and isolated in 72 % yield.

2.2 Preparation of 3-halo-pyrazolines.

The production of **3b** and **3c** were accomplished via a four-step process. The first two steps in the preparation of 3-halo-pyrazolines were the dialkylation processes in which the 1,3-diphenyl-propane-1,3-dione was dialkylated by methyliodide to get 2,2-dimethyl-1,3-diphenyl-propanedione(**1**), which resulted in 94% yield. Then, a condensation reaction of **1** with hydrazine

resulted in the formation of 4,4-dimethyl-3,5-diphenyl-4H-pyrazole (**2**) in 97% yield. The final steps were the preparation of **3b** and the synthesis of **3c** in 91% and 29% respectively (Figure 17). This was accomplished by treating the corresponding 4,4-dimethyl-3,5-diphenyl-4H-pyrazole (**2**) first with methyllithium followed by p-toluenesulfonylchloride (Ts-Cl) or p-toluenesulfonylbromide (Ts-Br) respectively.

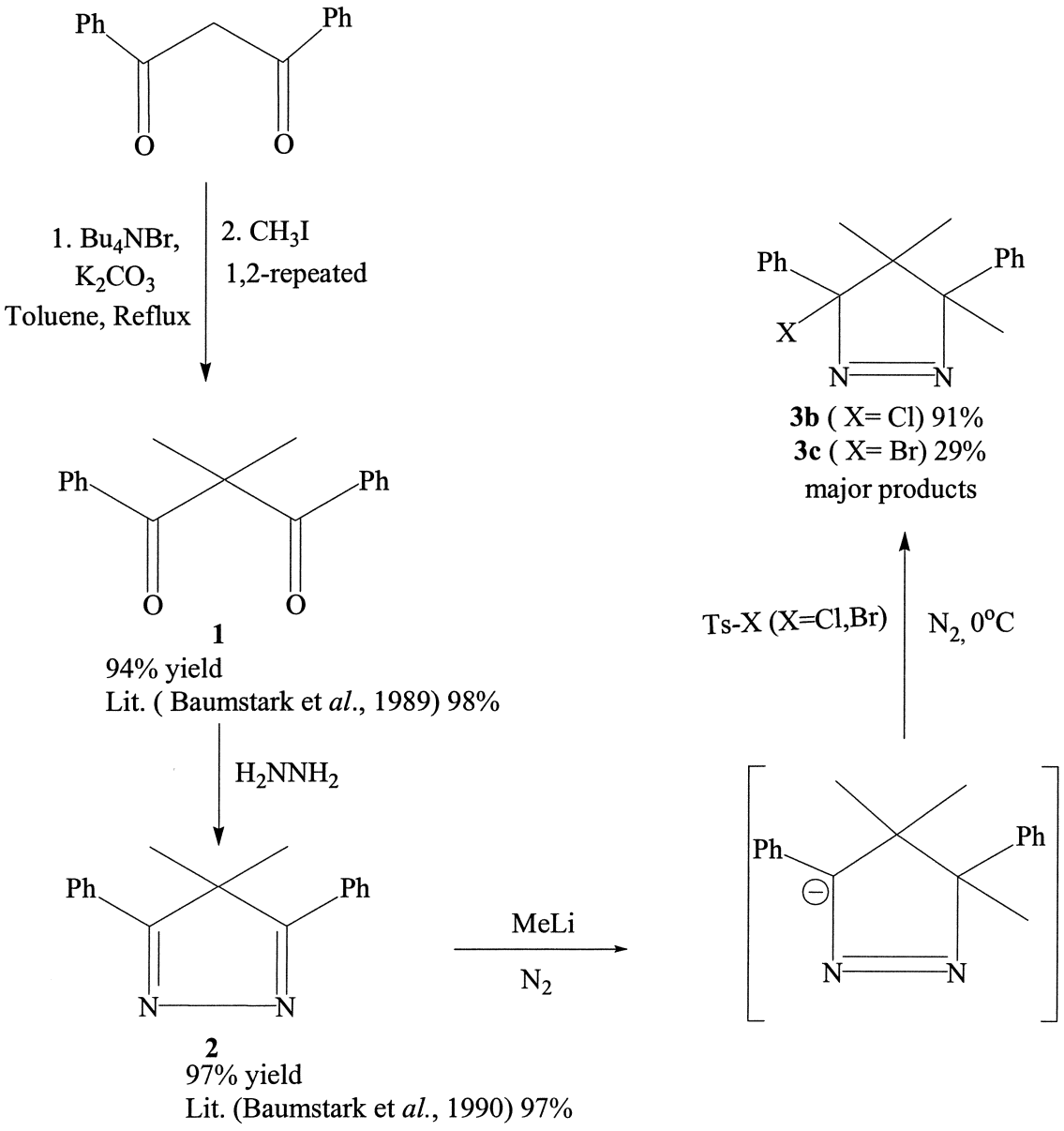


Figure 17. Four step process for the preparation of **3b** and **3c**.

The level of purity of **3b** and the synthesis of **3c** were verified by $^{1}H,^{13}C$ NMR, GC-MS data, narrow range of melting point and C,H,N-analysis. The ^{1}H NMR spectra of both **3b** and **3c** showed signal for one of the methyl of 4,4-dimethyl group up-field from that of the Tetramethylsilane (TMS) according to the expectation.

New compound, 4,4,5-trimethyl-3,5-diphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**4**), was isolated as a minor product in 8% yield during the preparation of **3b** (Figure 18). The procedure for the synthesis of **3c** also resulted in the formation of a small amount of **4** that was only detected by TLC.

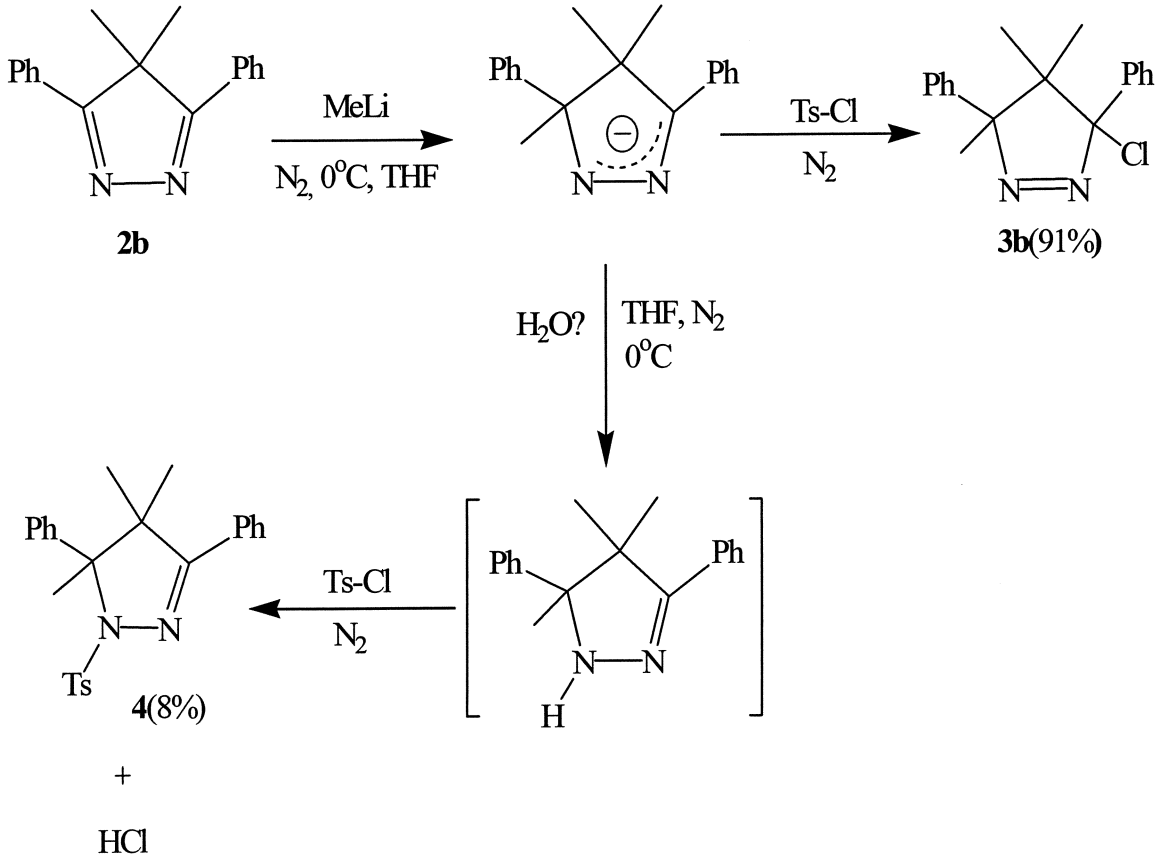


Figure 18. The formation of **4** is suggested to occur via an N-hydrated intermediate *in situ*.

Compound **4** was also prepared in 82% yield in our lab during a reaction of the lithium salt of 3,4,4-trimethyl-3,4-dihydro-3,5-diphenyl-2H-pyrazole *in situ* with p-toluenesulfonylfuloride. It was also suggested that the pathway to the formation of **4** using Ts-F should be different from that of using the Ts-Cl (Figure 19).

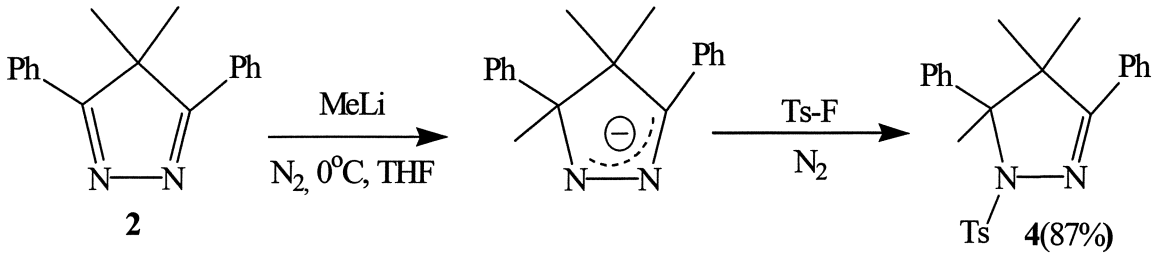
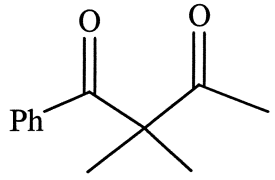
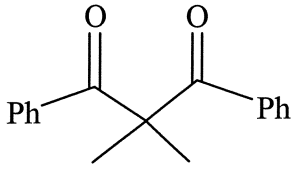
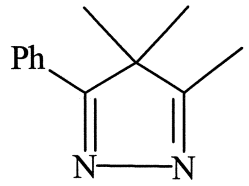
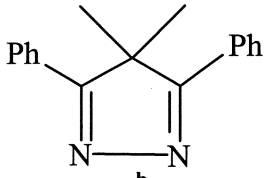
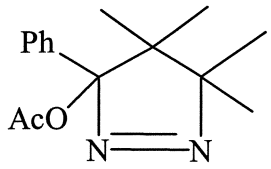
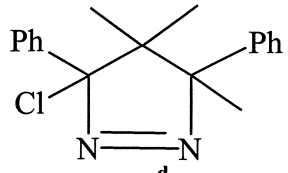
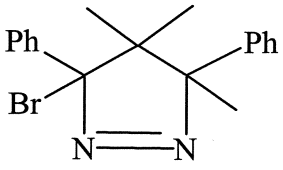
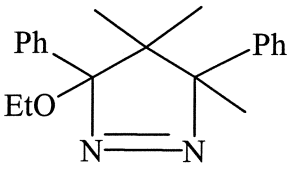
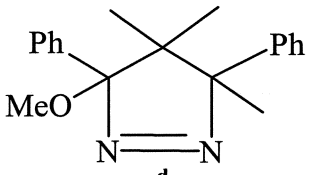
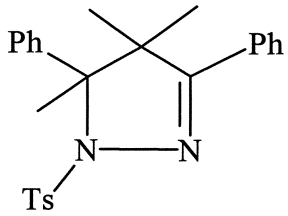
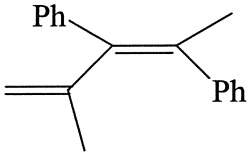
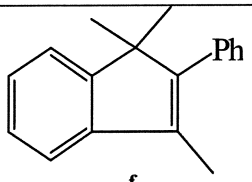


Figure 19. Compound **4** was produced in good yield when Ts-F was used as a tosylating agent.

Table 1. Summary of percent yields and melting point values for compounds that have been prepared or synthesized in this project in comparison with literature values.

Compound	% Yield	M.P (°C)	Lit. % Yield	Lit. M.P (°C)
 **1a**[a]	93	82-83	96	81-83
 **1**[a]	94	95-96	98	95-96

 **2a**[b]	92	94-95	93	94-95
 **2**[b]	97	126-127	97	127-128
 **3a**[c]	2*	101-103	63	102-104
 **3b**[d]	91	122-123	92	123.5-124.5
 **3c**	29	146-147	N/A	N/A
 **3d**	68	74-76	N/A	N/A

 **3**[d]	80	98-99	22/63	101-103
 **4**	(8)82	169-171	N/A	N/A
 **8**[e]	51	oil	93	oil
 **9**[f]	96	Semi-oil	18[f]	72 [f], 82 [g]

Literature reference: [a] (Baumstark, et *al.*, 1989), [b] (Baumstark et *al.*, 1990), [c] (Kennedy et *al.*, 1991) [d] (Kennedy et *al.*, 2004), [e] (Jutta et *al.*, 1999), [f](Anke,1985), [g] (Wayne,1974). N/A = Unpublished,* low result was obtained due to the presence of fortuitous O_2 in the reaction mixture.

2.3 Kinetics

The thermolysis of compounds **3b** and **3c** were monitored over several half-lives by ^1H NMR spectroscopy at constant temperature in a silicon oil bath (±1°C). The rate of disappearance of pyrazoline was found to be identical to the rate of appearance of the product and *vise versa*. Discoloration was observed during the thermolysis. The first order rate constants (k_1) for the thermal decomposition of **3b** and **3c** at 150 °C were found to be 7.3 ± 0.8 x 10^{-5} s^{-1} and 42.3 ± 1.6 x 10^{-5} s^{-1} respectively. First order rate constant values for the thermolysis of **3b**

and **3c** determined over a 30° and 50° temperature ranges. The deviation (error) values of the first order rate constants were calculated at a 95% confidence limit with the aid of a PSI plot program. The ± 5-10% errors obtained were reasonable for this type of rate constant determination. Figures 20 to 25 show the data plot that was important in the determination of k_1 from thermal decomposition of **3b** at various temperatures. The kinetic data are summarized in Table 2.

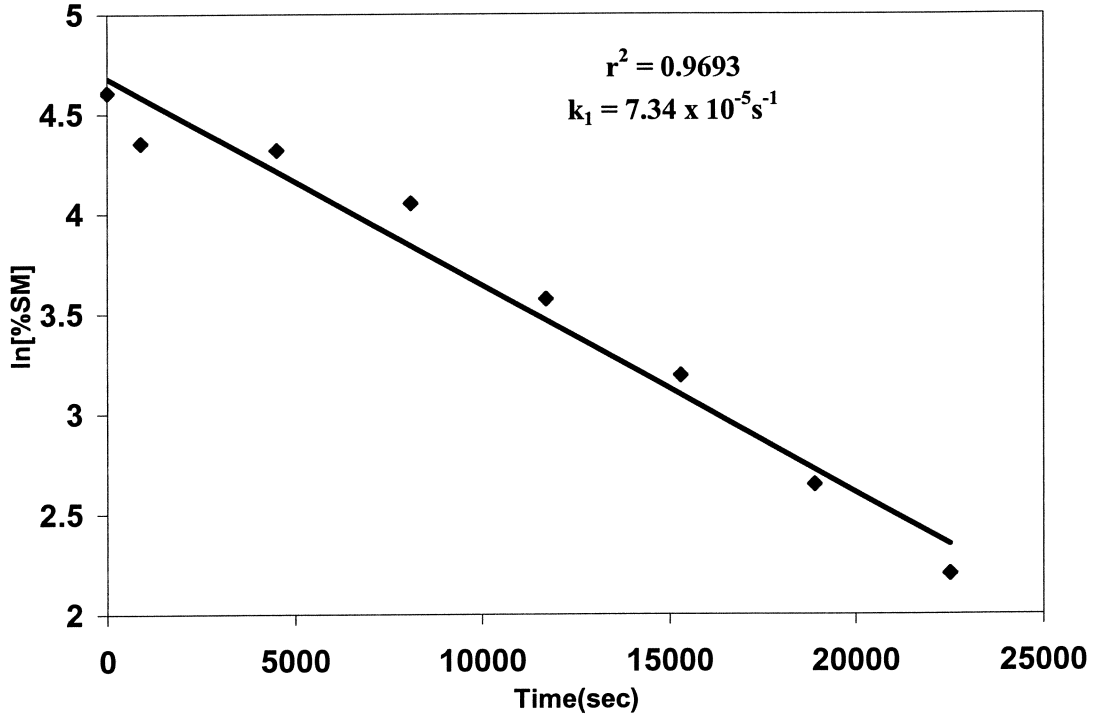


Figure 20. Plot of ln[%SM] vs. time (sec) for the thermolysis of 3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H pyrazole (**3b**) in 1,3-dibromobenzene at 150 ° C.

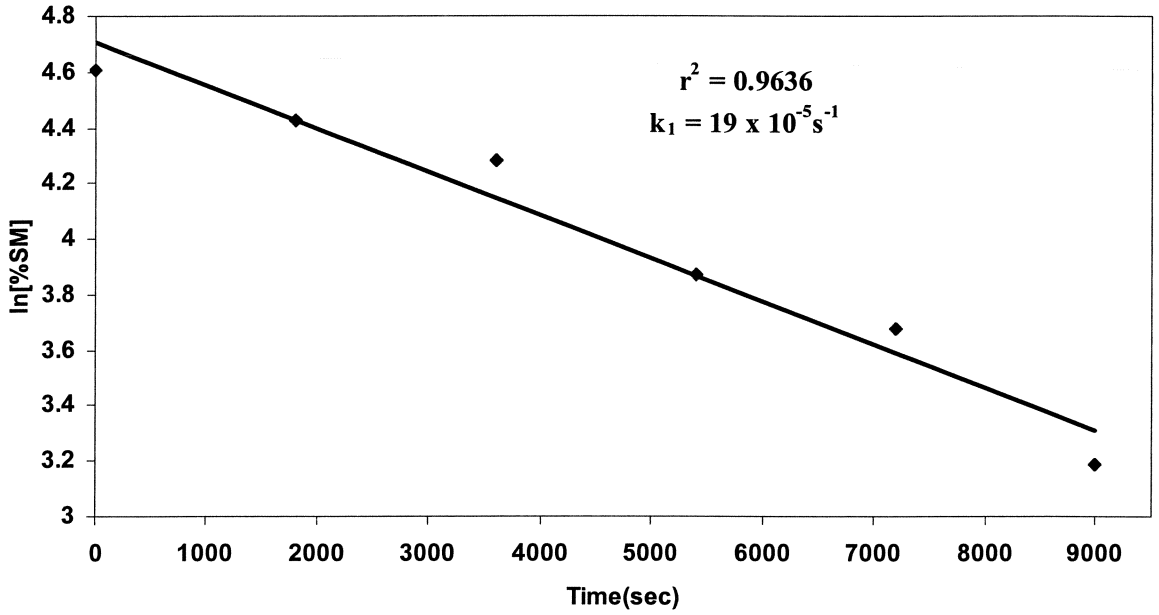


Figure 21. Plot of ln[%SM] vs. time(sec) for the thermolysis of 3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3b**) in 1,3-dibromobenzene at 155 °C.

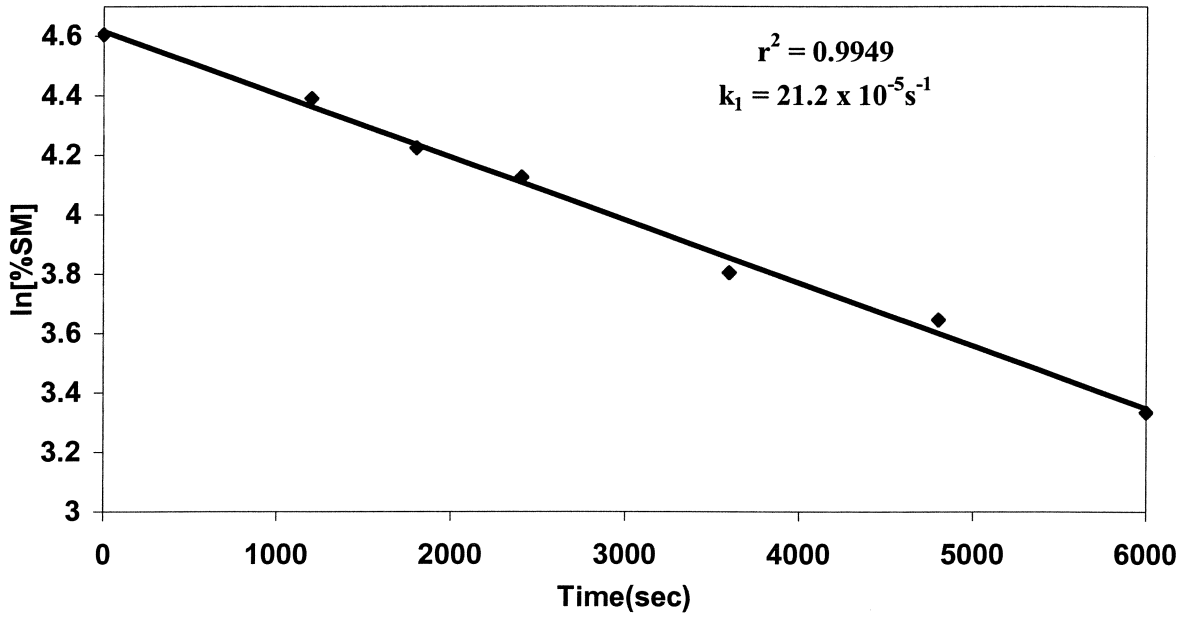


Figure 22. Plot of ln[%SM] vs. time (sec) for the thermolysis of 3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3b**) in 1,3-dibromobenzene at 160 °C.

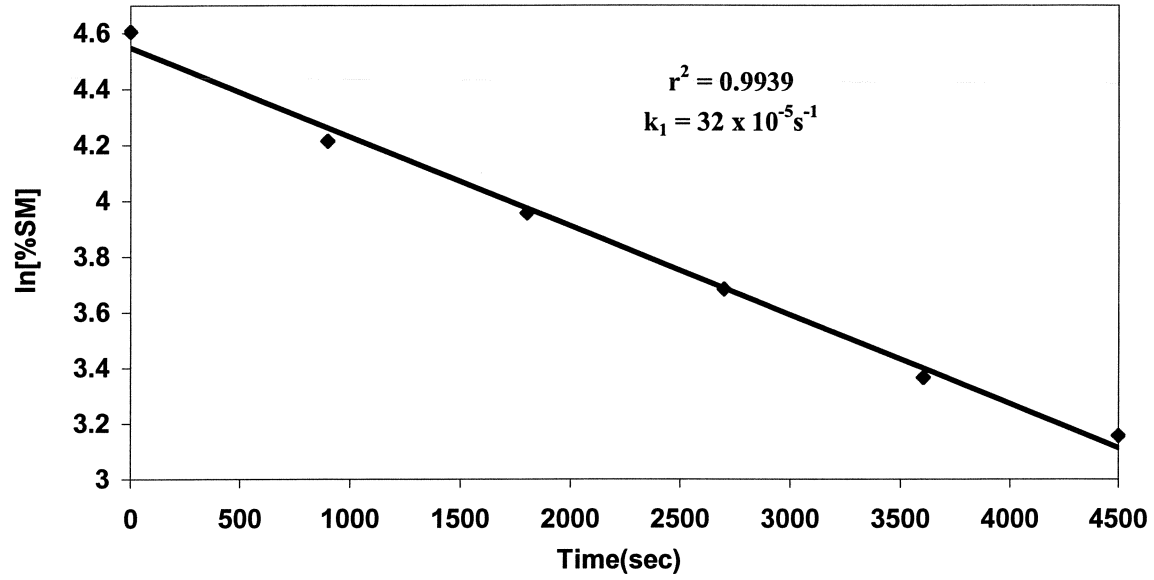


Figure 23. Plot of ln [%SM] vs. time (sec) for the thermolysis of 3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3b**) in 1,3-dibromobenzene at 165 °C.

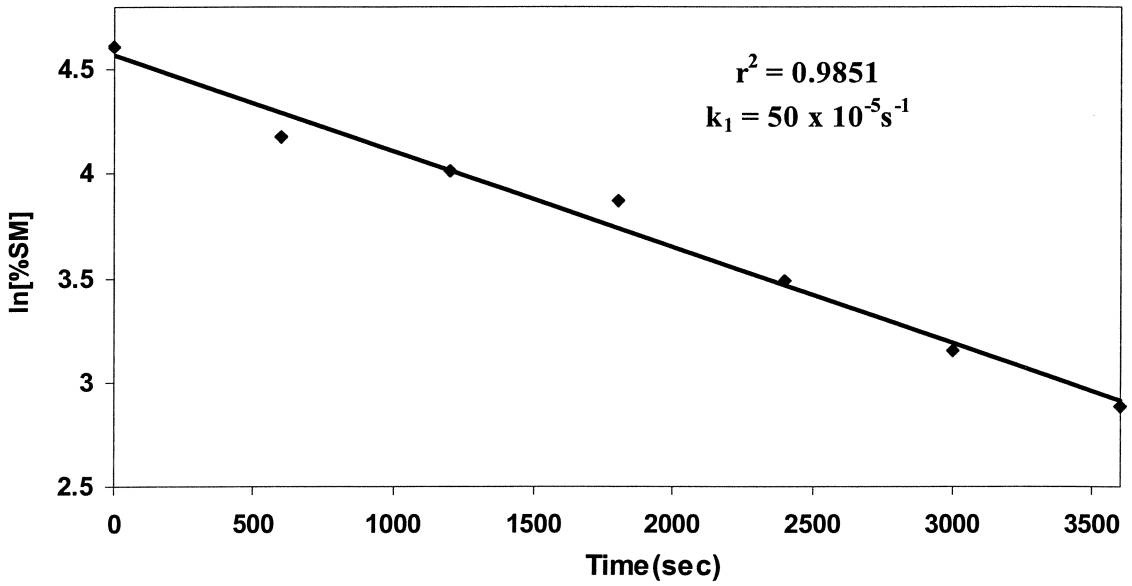


Figure 24. Plot of ln [%SM] vs. time (sec) for the thermolysis of 3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3b**) in 1,3-dibromobenzene at 170 °C.

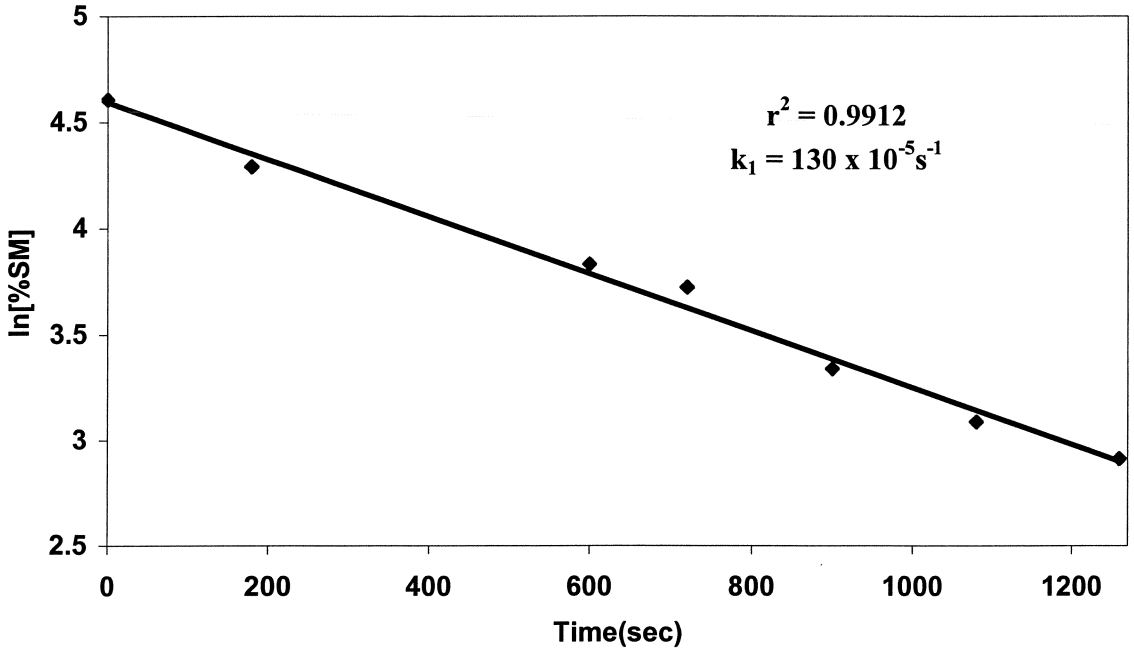


Figure 25. Plot of ln [%SM] vs. time (sec) for the thermolysis of 3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3b**) in 1,3-dibromobenzene at 180 °C.

Table 2. A summary of first order rate constants for the decomposition of **3b** (30-degree temperature range) in 1,3-dibromobenzene.

Compd.#	Temp. ± 1°C	$k_1(s^{-1}) \times 10^{+5}$	Rel.rate
3b	150	7.3 ± 0.8	1
3b	155	19 ± 2.0	3
3b	160	21 ± 0.7	3
3b	165	32 ± 1.3	4
3b	170	50 ± 3	7
3b	180	130± 6	18

The thermolysis of **3c** was conducted over a 50° range of temperature from 110°C to 160°C. The first order rate constant values were determined from the slope of ln[%SM] vs. time

(sec) plots. All plots showed good correlation coefficients. Figures 26-30 are representative plots for the thermal decomposition of **3c** at 110°C to 160°C. The kinetic data are summarized in Table 3.

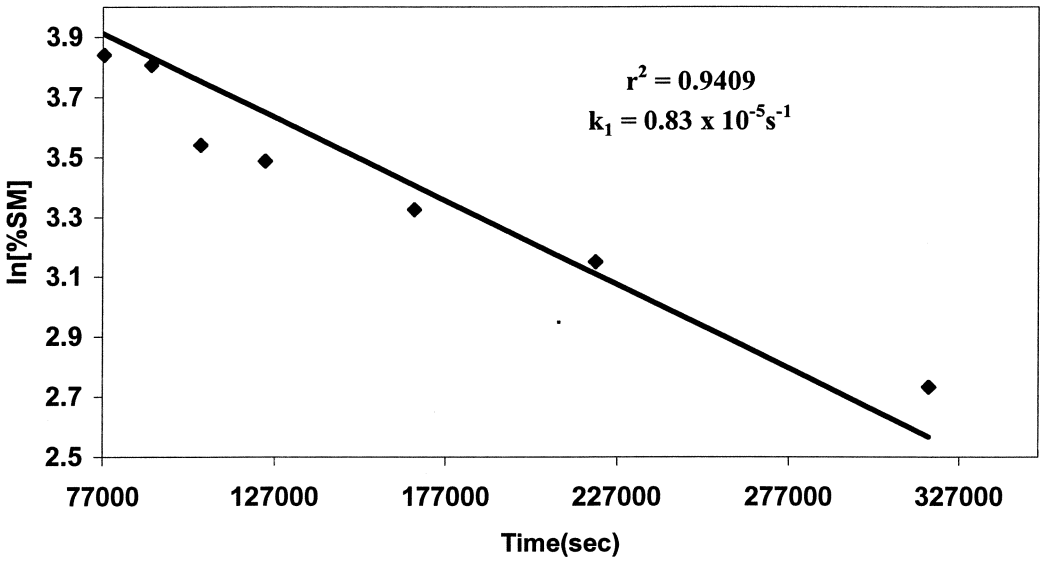


Figure 26. Plot of ln[%SM] vs. time (sec) for the thermolysis of 3-bromo-4,4,5-trimethyl-3, 5-diphenyl-4,5-dihydro-3H-pyrazole (**3c**) in 1,3-dibromobenzene at 110°C.

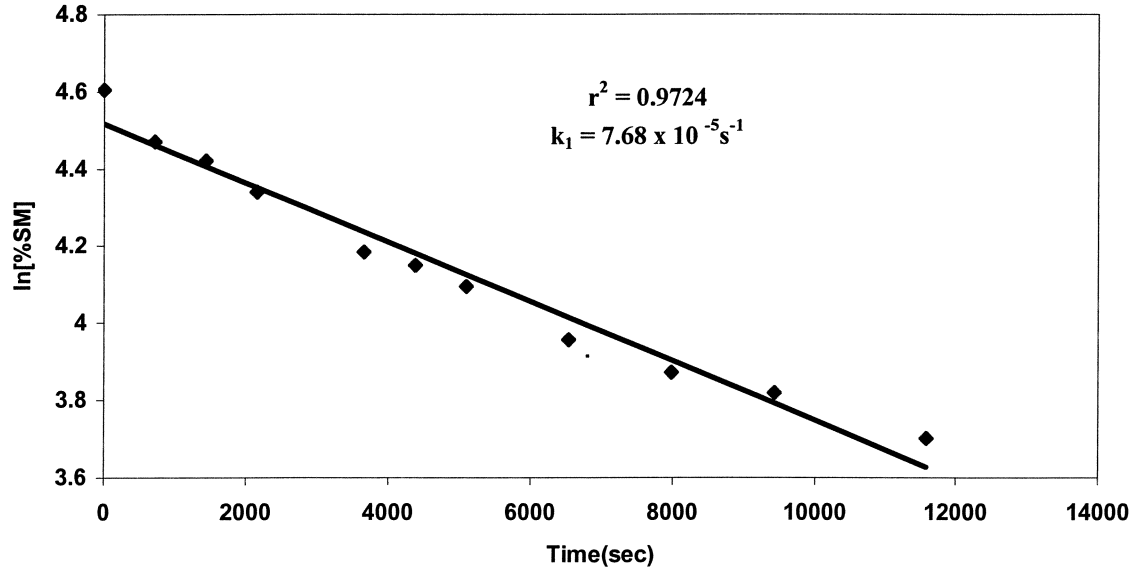


Figure 27. Plot of ln[%SM] vs. time for the thermolysis of 3-bromo-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3c**) in 1,3-dibromobenzene at 130 °C.

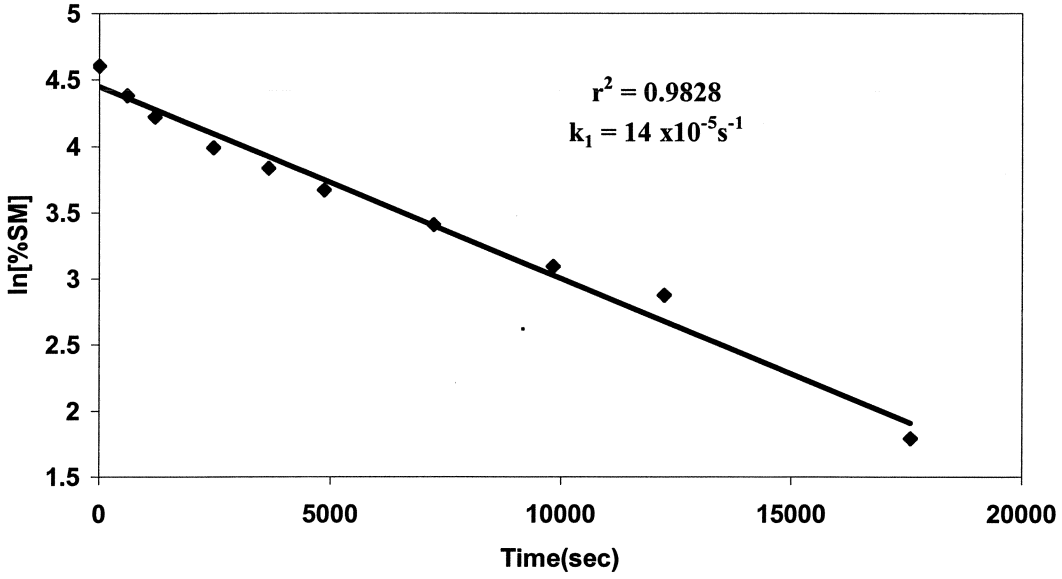


Figure 28. Plot of ln[%SM] vs. time (sec) for the thermolysis of 3-bromo-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3c**) in 1,3-dibromobenzene at 140 °C.

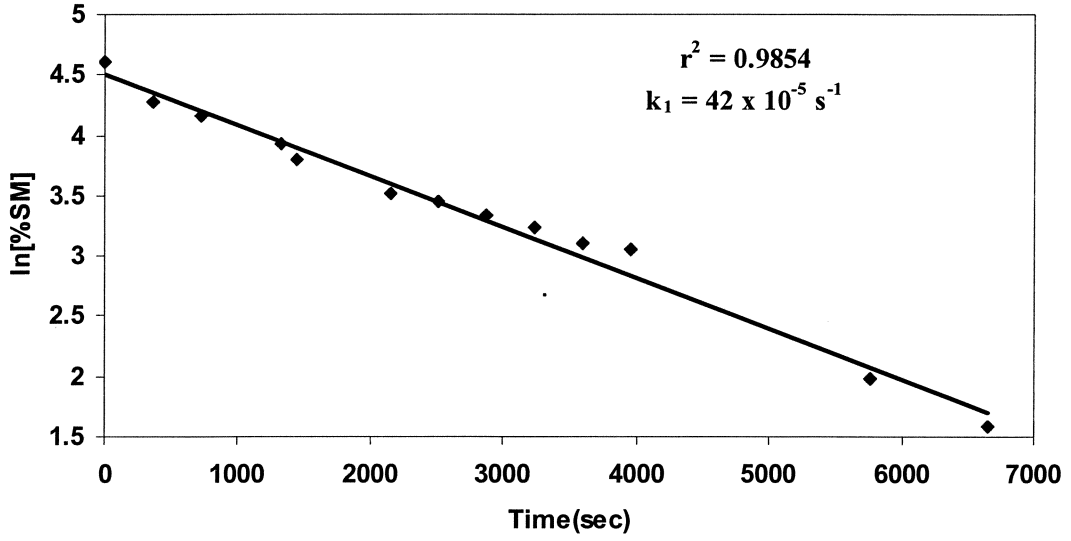


Figure 29. Plot of ln[%SM] vs. time (sec) for the thermolysis of 3-bromo-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3c**) in 1,3-dibromobenzene at 150°C.

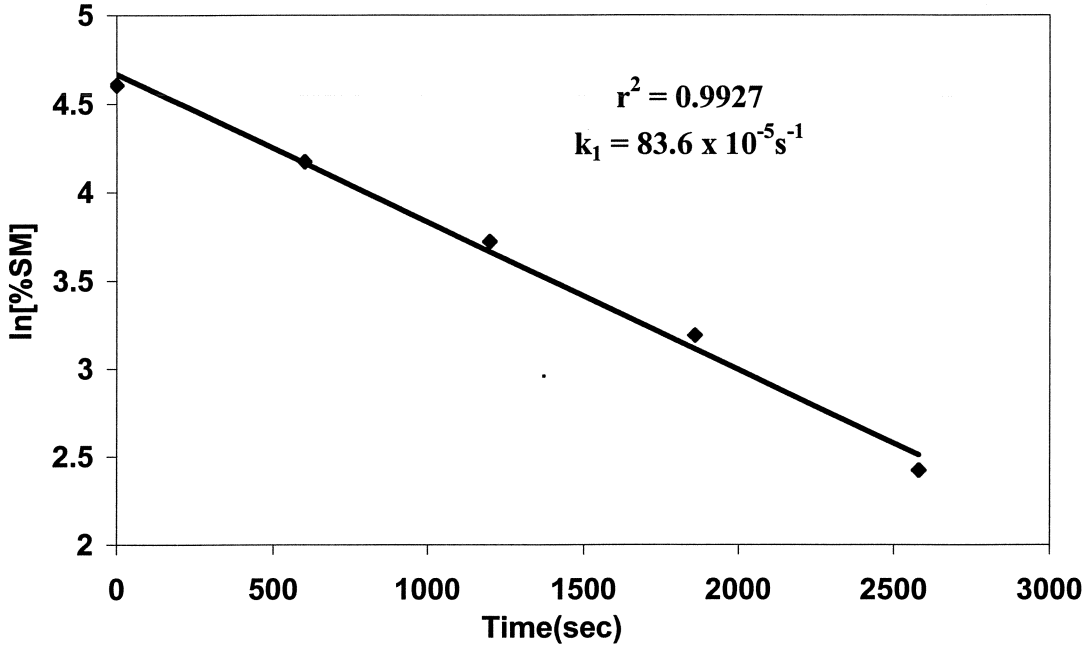


Figure 30. Plot of ln[%SM] vs. time (sec) for the thermolysis of 3-bromo-4, 4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3c**) in 1,3-dibromobenzene at 160 °C.

Table 3. Summary of first order rate constants for the decomposition of **3c** (50° range) in 1,3-dibromobenzene.

Compd.#	Temp. ± 1°C	$k_1 \times 10^5 (s^{-1})$	Rel.rate
3c	110	0.83 ± 0.04	1
3c	130	7.68 ± 0.26	9
3c	140	14.0 ± 0.68	17
3c	150	42.0 ± 1.6	51
3c	160	83.6 ± 4	101

The kinetic data for **3b** and **3c** were plotted using the Eyring approach (Laidler et *al.*, 1999) to determine the $\Delta H^{\ddagger}$'s (Figure 31 and 32). The activation parameters for the thermolysis of **3b** were: $\Delta H^{\ddagger}$ = 32.9±1.0 kcal/mol, $\Delta S^{\ddagger}$ = -2.4±0.07 eu, $\Delta G^{\ddagger}$ = 33.9kcal/mole, $k_{150^{\circ}C}$ = 7.3±0.8

X 10^{-5} s^{-1}. For **3c** the activation parameters were: $\Delta H^{\ddagger}$ = 29.5±0.7 kcal/mol, $\Delta S^{\ddagger}$ = -6.9±0.03eu, $\Delta G^{\ddagger}$ = 32.4kcal/mol, $k_{150}{}^{o}{}_{C}$ = 42±1.6 x 10^{-5} s^{-1}. The enthalpy of activation values for the thermal decomposition of **3b** appeared to be slightly greater than that of **3c** but the experimental error must be viewed with cautions. The entropies of activation for thermolysis of **3b** and **3c** were –2.4eu and –6.9eu respectively and only differ by -4.5eu. Although there were only slight difference in $\Delta G^{\ddagger}$ value between **3b** and **3c,** the rate constant value of **3b** appears to be much lower than **3c**. This is because the rate constant value is dependant on $\Delta G^{\ddagger}$ (lnk = ln ($k_B T/h$) – ($\Delta G^{\ddagger}$/ J mol^{-1})/8.3145T/K). Results of first order rate constant values and activation parameters for the thermal decomposition of **3b** and **3c** are summarized in Table 4 & 5 respectively.

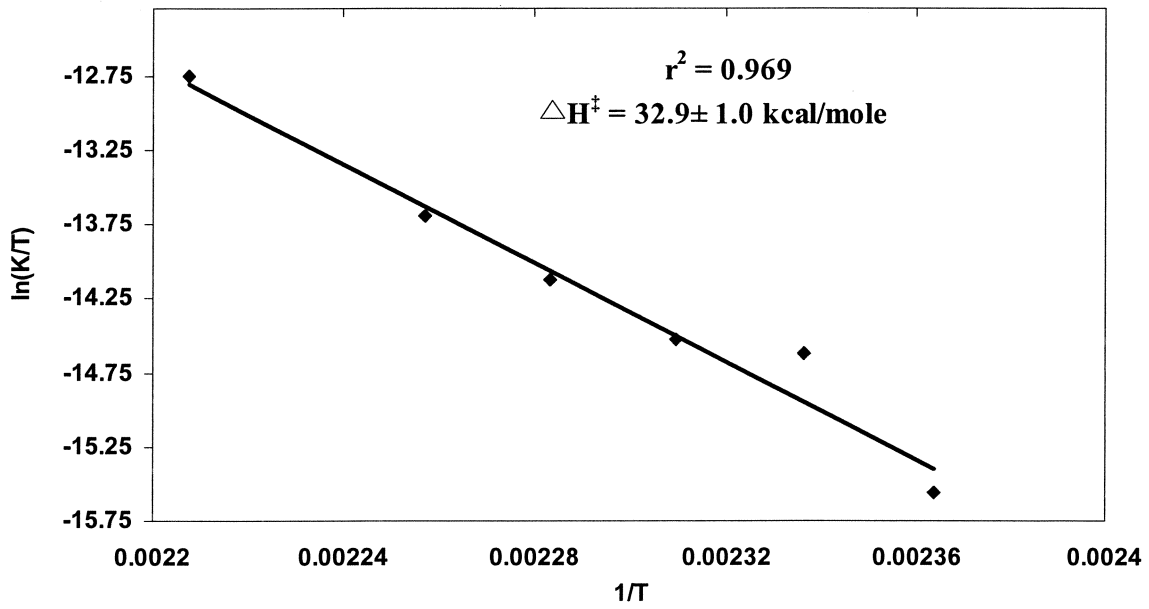


Figure 31. The determination of enthalpy of activation ($\Delta H^{\ddagger}$) for the thermolysis of 3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3b**) using the Eyring approach.

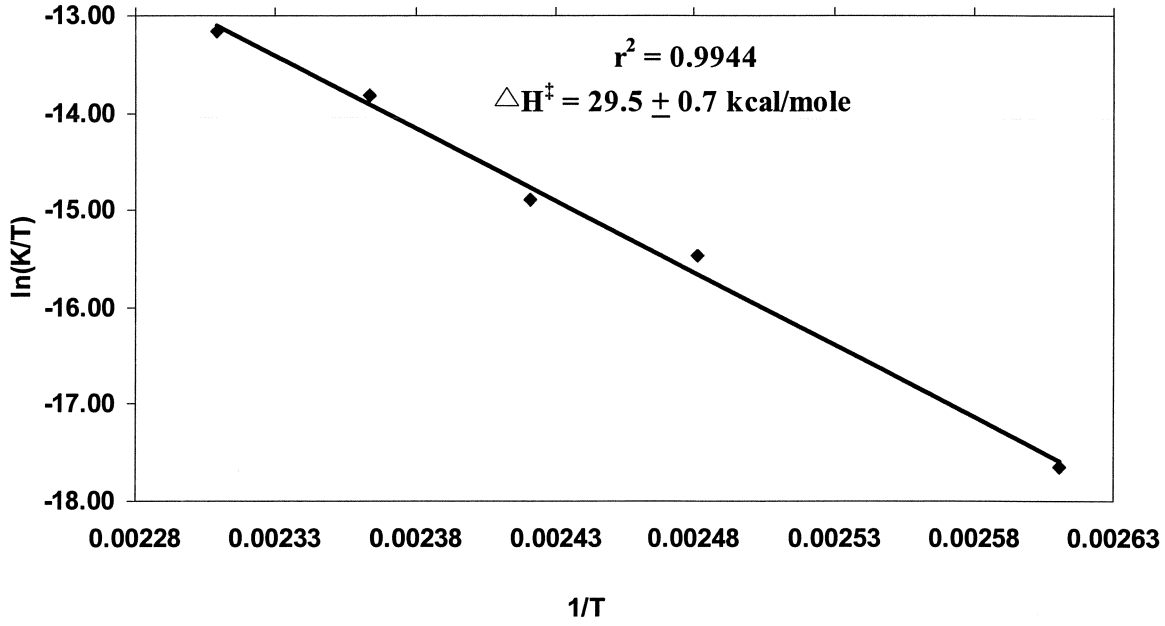
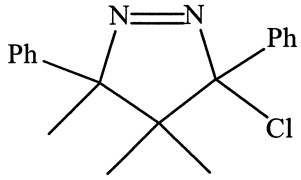
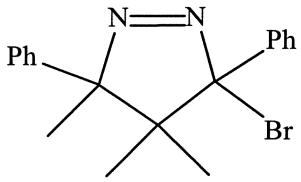


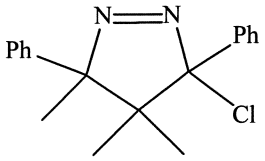
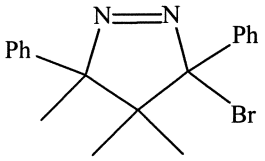
Figure 32. The determination of enthalpy of activation ($\Delta H^{\ddagger}$) for the thermolysis of 3-bromo-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**3c**) using the Eyring approach.

Table 4. Summary of rate constants of both **3b** and **3c.**

Compound	Structure	k_1 s^{-1} x 10^5	T±1°C	Solvent[a]
3b		7.3 ± 0.8	150	DBB
		19.0 ± 1.5	155	DBB
		21.2 ± 0.7	160	DBB
		32.0 ± 1.3	165	DBB
		50.0 ± 2.5	170	DBB
		130.0 ± 5.7	180	DBB
3c		0.8 ± 0.05	110	DBB
		7.7 ± 0.3	130	DBB
		14.0± 0.7	140	DBB
		42.0 ± 1.6	150	DBB
		83.6 ± 4	160	DBB

[a]DBB, 1,3-Dibromobenzene.Standard deviations were calculated in a 95% confidence limit using a PSI plot program.

Table 5. Summary of rate constants and kinetic parameters for the thermolysis of pyrazolines (**3b** and **3c**).

Compd.	Structure	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	$\Delta G^{\ddagger}(150^{\circ}C)$ (kcal/mol)	$k_1 s^{-1} \times 10^5$ (150 °C)
3b		32.9 ± 1.0	-2.4±0.07	33.9	7.3 ± 0.4
3c		29.5 ± 0.7	-6.9±0.03	32.4	42 ± 1

2.4 Product Studies

The product studies for the thermal decomposition of **3b-c** were carried out at high temperatures both neat (with out adding any solvent) and in DBB solvent. The first step in the product study was the thermolysis of **3b** in an extremely hot temperature (200°C). This temperature was chosen mainly because it helps to decompose the compound very quickly and provide results in a timely fashion. The thermal decomposition of 25mg of **3b** at 200 °C for 1-5min resulted in a shift of the ^{1}H NMR signal of the methyl group, which was *cis* with the two phenyls of the **3b**, toward the lower field region of the spectrum. This suggested that the starting material was converted into a new type of product, which was suggested (merely based on MS data due to difficulty of purification using regular chromatography method) to be a chlorinated cyclopropane product. However, a continuation of heating at 200°C for 8h, resulted in olefinic

product, which was identified as 2,3-diphenyl-4-methyl-1,3-pentadiene (**8**) by comparing to the literature (Padwa *et al.,* 1983; Jutta et *al.*, 1999). The thermal decomposition of 100mg of **3b** (25mg/NMR tube), was dissolved in DBB and heated at 150°C for 12h and at 130°C for days, also resulted in **8** in 51% yield. The formation of what appeared to be isomers of **8** has also been detected in the ^{1}H NMR spectrum but none of the isomeric products was neither separated nor characterized. In addition to that, neat solid thermal decomposition of **3b** at 150°C for 15h or at 200°C for 8h produced **8**. Further heating of **8** at 150°C or 200°C in the presence of acid, *in situ*, for several days resulted in 1,1,3-trimethyl-2-phenylindene (**9**) with a 96% yield. Figure 33 is the proposed mechanistic explanation of the process of the thermal decomposition of **3b** both neat and in DBB solvent.

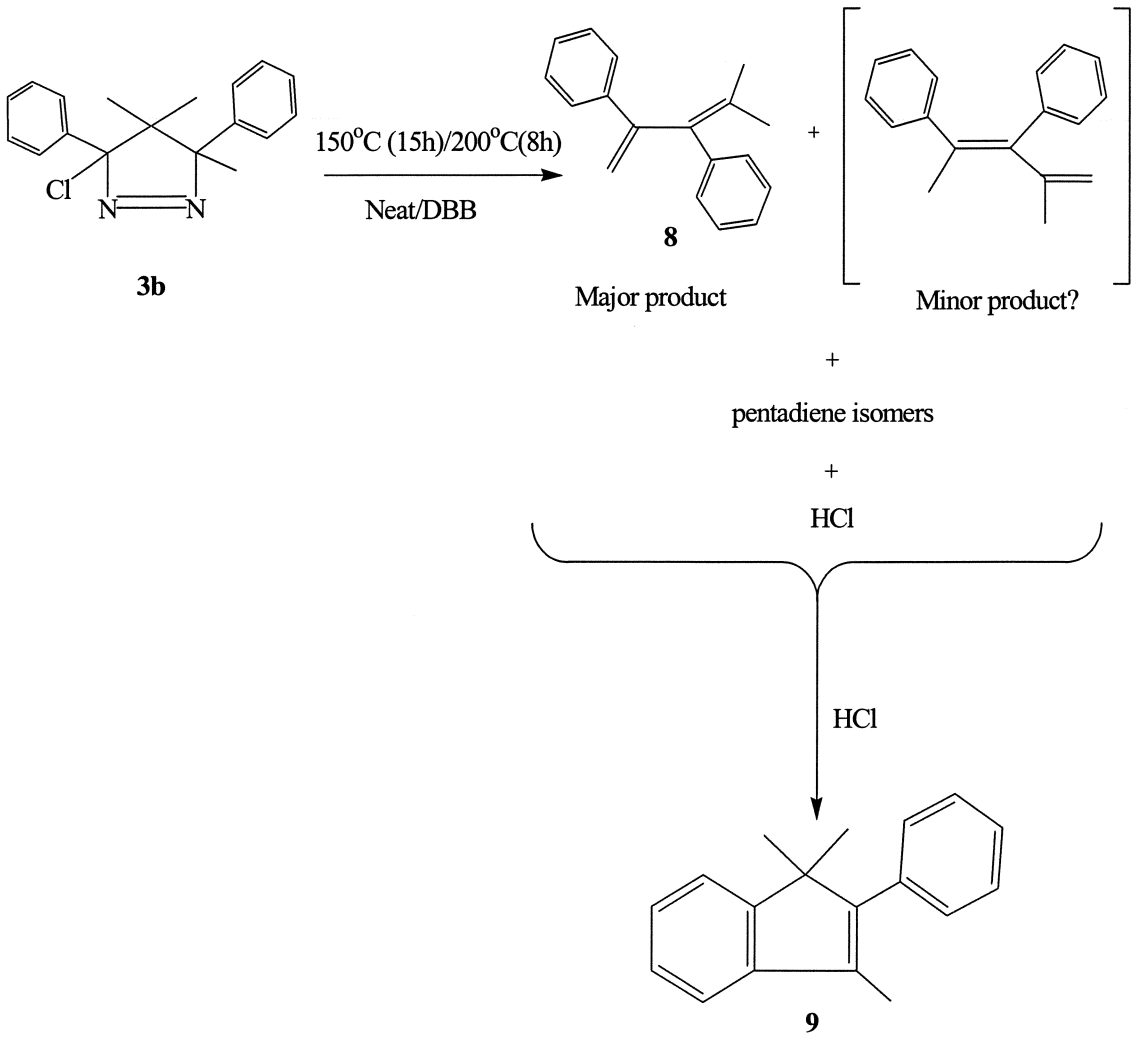


Figure 33. Thermal decomposition of **3b** both neat and in DBB resulted in **8** as a major intermediate product (51% yield). Up on continues heating in the presence of an acid; the end product **9** was able to be isolated in 96% yield.

Further experiment was carried out to check the acid catalyzed process of the conversion of **8** to **9**. Into a high- pressure test tube, **3b** was dissolved in DBB and excess of quinoline was added. The solution mixture was degassed with argon and the tube was sealed immediately. Heating of the tube at high temperatures (150°C or 200°C) resulted in the production of **8** and its isomers. The continued heating of the test tube that contained compound **8** did not result in **9**. However, upon an addition of excess of an acid, the tube was again heated for longer time and

compound **9** was formed as a final product. The reason of adding an acid was to neutralize the base and create an acidic media that was crucial in the transformation of **8** to **9** (Figure 34).

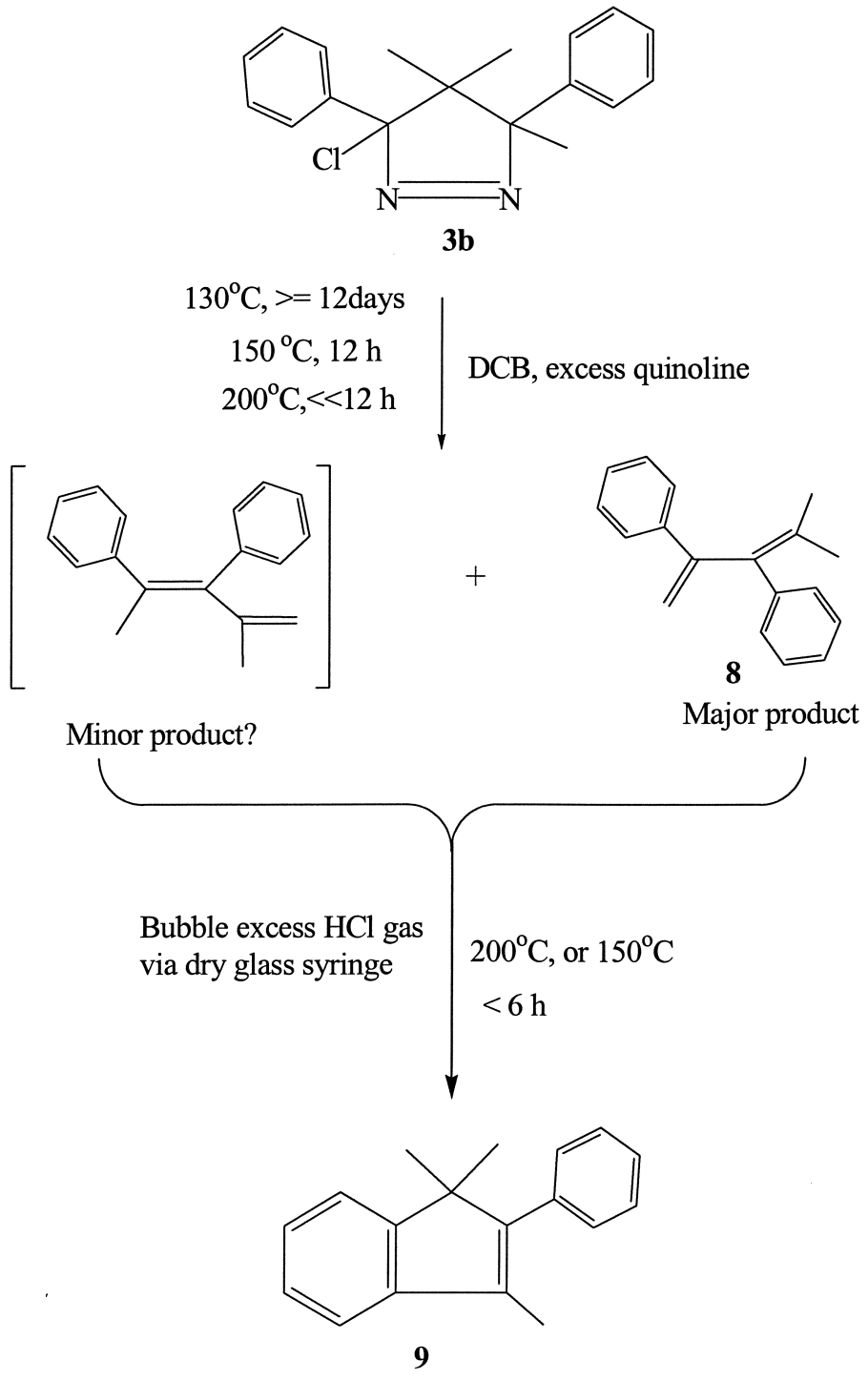


Figure 34. The conversion of **3b**, which was first treated with quinoline, into indene **9** was facilitated by the addition of excess HCl gas.

2.5 Kinetic Study of the Thermal Decomposition of 3b in the Presence of Quinoline.

The first order rate constant value for the thermal decomposition of **3b** at 150°C in the presence of excess quinoline was determined. The value of k_1 at 150°C was found to be 7.9 ± 0.1 x $10^{-5}s^{-1}$, and it was comparable to the value of rate constant determined without the addition of quinoline k_1 = 7.34 ± 0.8 x $10^{-5}s^{-1}$(Figure 35). Since thermal decomposition of **3b** before and after the addition of quinoline did not bring significant difference in rate constant value, the formation of an intermediate product **8** appeared not to be an acid catalyzed process.

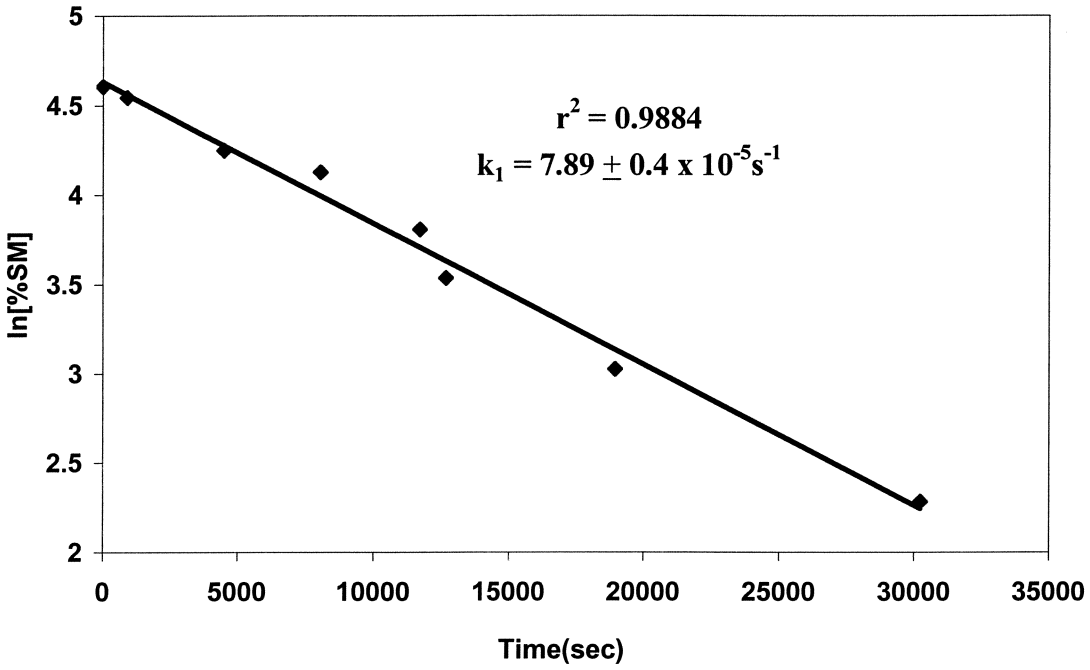


Figure 35. Plot of ln[%SM] vs. time for the thermolysis of **3b** at 150°C in the presence of excess quinoline.

2.6 Thermal decomposition of 3c neat, in non-polar and protic solvents

The thermal decomposition of **3c** was carried out neat, and in solvents: DCB/DBB, cyclohexane or toluene. The thermal decomposition of **3c** in methanol produced **3** in poor yield via an ionic pathway. On the other hand, thermal products of **3c** in toluene and cyclohexane resulted in a β,γ-unsaturated ketone in minor isolated product. The formation of this ketone was confirmed by analyzing data only from ^{1}H NMR, MS and comparing it with the literature (Baumstark et *al.*, 1991). However, due to lack of time, none of products from the thermolysis of **3c** was fully characterized.

2.7 Thermal decomposition of 3b in protic solvents.

The formation of **8** from the thermal decomposition of **3b** was very intriguing because the product obtained was against what originally was expected. Therefore, the mechanistic pathway to the formation of **8** was carefully analyzed. The thermal decomposition of **3b** was carried out in protic solvents (methanol, ethanol) in an attempt to get information on the mechanism for the formation of **8** during thermolysis of **3b** in DBB.This experiment was carried out using the following key step. In a high-pressure tube,100mg of **3b** was dissolved in dry methanol and refluxed at 135±2°C for 12h. The ^{1}H NMR signal of the thermolysis product suggested a product that is identical to signals reported for 3-methoxy-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazoles (**3**) in 80% yield. Another experiment was set up for the thermolysis of **3b** in methanol, but at this time instead of decomposing the starting material in a hot silicon oil bath for 12h at 135±2 °C, the mixture was allowed to reflux to 24h which provided *cis/trans* cyclopropanes products in whose major product was corresponded to the retention of stereochemistry with *cis/trans* ratios of 4:1. These two products *cis*-1-methoxy-2,3,3-trimethyl-1,2-

diphenylcyclopropane (**5b**) and *trans*-1-methoxy-2,3,3-trimethyl-1,2-diphenylcyclopropane (**5c**) products were not isolated and characterized but results was obtained from ^{1}H NMR and MS data (Figure 36).

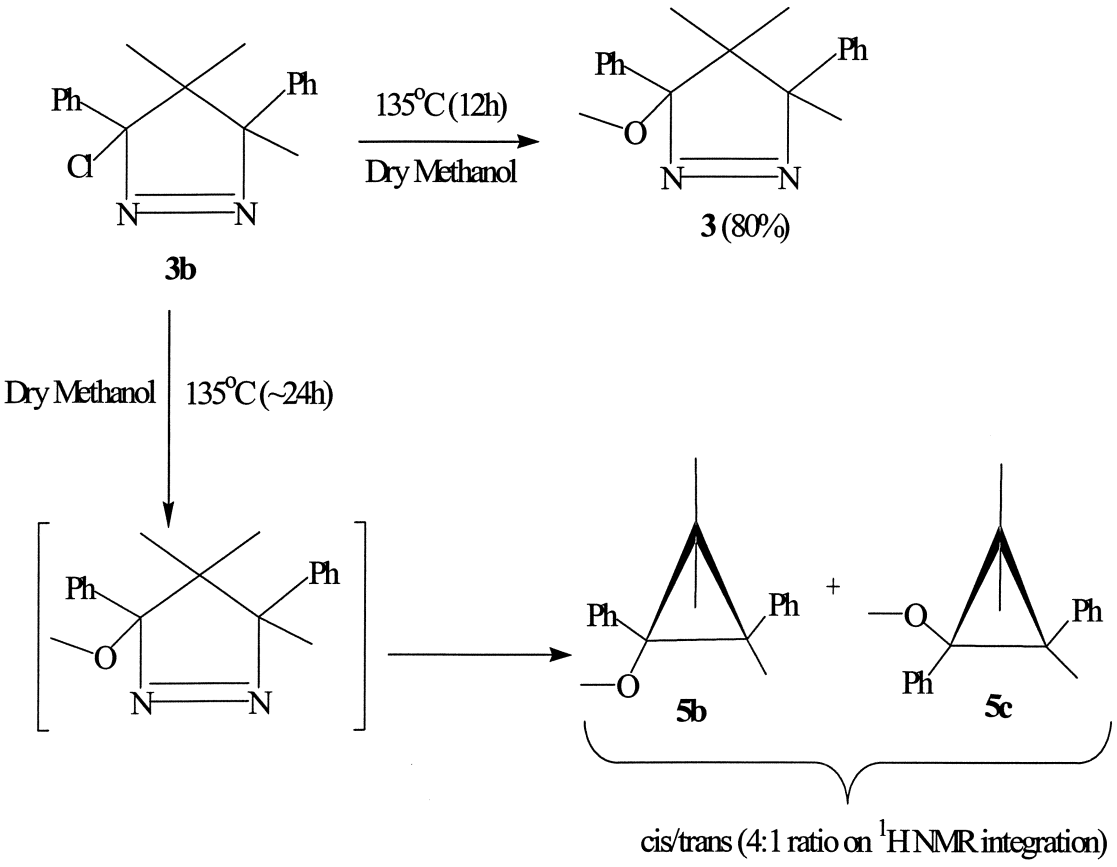
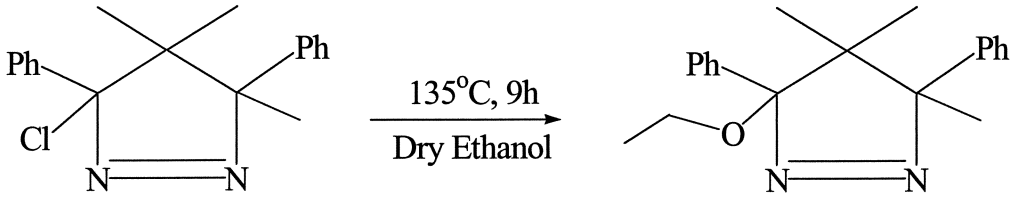


Figure 36. The thermolysis of **3b** in methanol was found to be an alternative method for the preparation of **3**, **5b** and **5c**.

Heating of **3b** at 135°C in dry ethanol for 9h resulted in the synthesis of 3-ethoxy-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazoles (**3d**) in a 68% yield (Figure 37), However, this result was only verified by ^{1}H NMR and MS data. There were also attempts and plan in carrying out a product study experiment in the thermolysis of **3d**. Although preliminary data from the

mass spectrum and ^{1}H NMR suggested of a production of an ethoxy added cyclopropane product, due to lack of research time, no complete evidence is available.



3b **3d (66%)**

Figure 37. The reflux of **3b** in ethanol resulted in the synthesis of **3d**.

CHAPTER III

DISCUSSION

3.1 Potential factors for the synthesis of N-tosylated pyrazole (4).

4,4,5-Trimethyl-3,5-diphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole(**4**) was synthesized both in minor and major yields using Ts-Cl and Ts-F as the reacting reagents. A similar study in the past (Engle,1976) indicated that the formation N-hydrated intermediate is the key step in the formation of **4** from a reaction between pyrazoline and Ts-Cl. It is therefore reasonable to generalize that compound **4** was isolated mainly due to reaction of 4,4-dimethyl-3,5-diphenyl-4H-pyrazole (**2**) with Ts-Cl via the formation of N-hydrated intermediate *in situ*. On the other hand, reaction between the N-anionic pyrazoline and Ts-F resulted in the formation of **4** in major yield, possibly via a reaction of nitrogen with sulfur in Ts-F (Figure 39). The main reason for getting a high yield when **2** reacts with Ts-F instead of Ts-Cl is that fluorine is more electronegative than chlorine and there is a lesser chance that the negative charge on the carbon or nitrogen atom of the pyrazoline intermediate *in situ* can pull another strongly electronegative atom of fluorine from the Ts-F. For this reason, the only plausible route for the formation of **4** as a major product is the reaction between the N-anion of the pyrazoline with sulfur from the tosylate group of the Ts-F followed by the leaving of the fluorine (Figure 39).

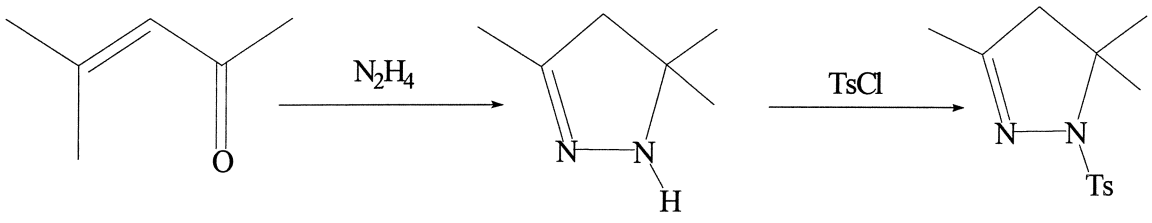


Figure 38. 1H-pyrazole is shown to be an intermediate product in the formation of N-tosylated 1H-pyrazoles (Paul et *al.*, 1976).

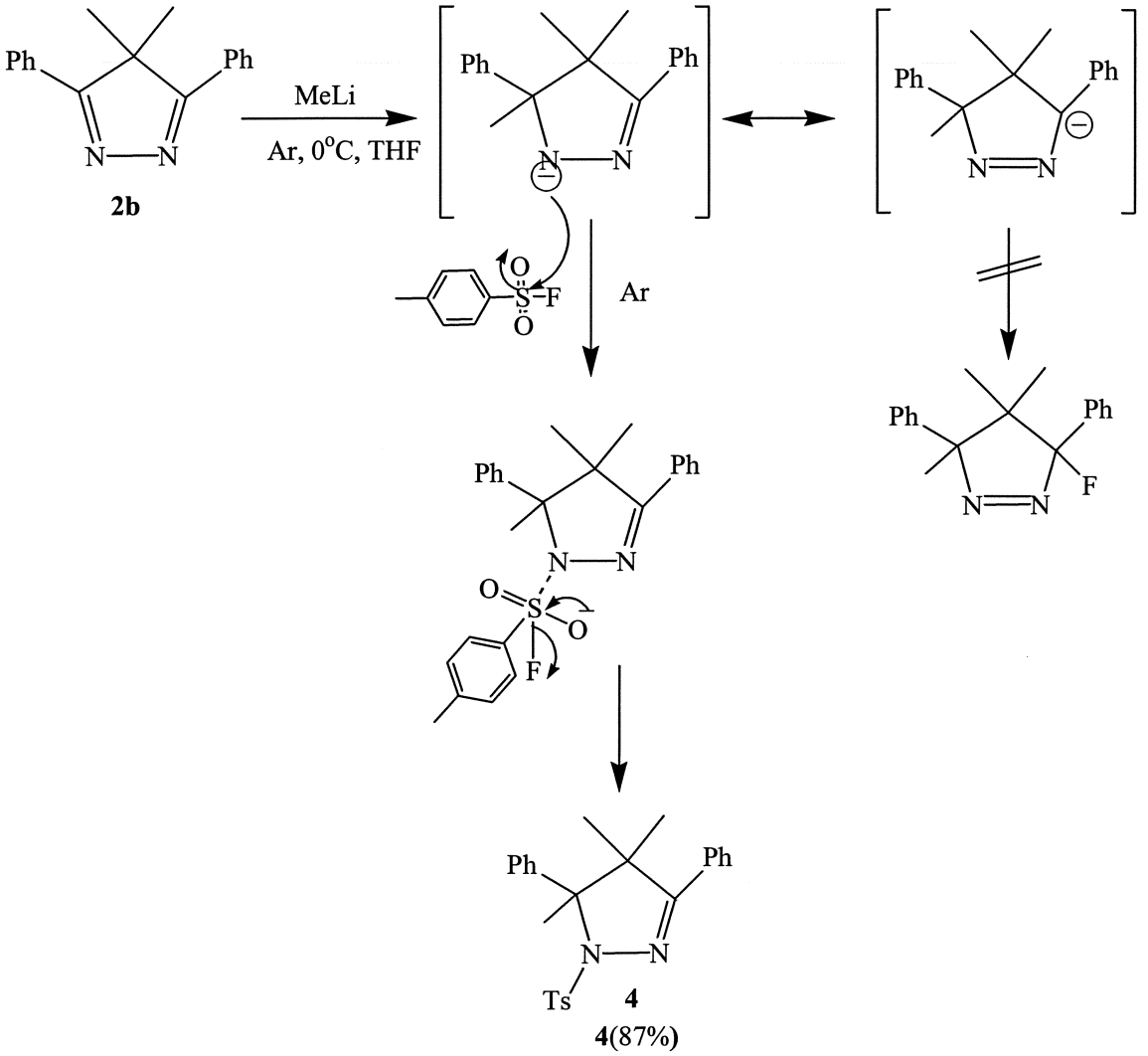


Figure 39. A proposed mechanism for the synthesis of **4**.

3.2 Thermolysis of 3b-c and the determination of activation parameters

Recently, halogenated pyrazolines (**3b-c**) were thermolyzed in an attempt to isolate halogenated cyclopropane products. The thermal decomposition of **3b** in DBB resulted in an intermediate product **8** via the rearrangement of a possibly unstable cyclopropane intermediate. We did not find conclusive evidence about the formation of cyclopropanes; however, sample taken after a brief thermal decomposition of **3b** in hot silicon oil and checked in the MS

spectroscopy provided the mass value that corresponded to the mass of a cyclopropane product. An attempt to get more evidence from other characterization methods such as ^{1}H NMR, ^{13}C NMR *etcetera* was not a success which is possibly due to the instability of the presumed cyclopropane product on a silicagel during the purification process. Moreover, much of an attention was given to a process in identifying a pathway in the formation of an intermediate product **8** and the final end product **9**.

The thermal decomposition of quinoline added **3b** at high temperature resulted in the formation of a single product **8**. Later, passing of hydrogen chloride gas through a solution of **8** and the continuous of thermal decomposition in hot silicone oil bath resulted in the formation of **9,** providing strong evidence for an acid catalyzed step of the conversion of **8** to **9**. The production of both **8** and **9** were characterized by $^{1}H,^{13}C$ NMR and mass spectral data (Vasquez et *al.*, 2004, unpublished data). Then, the spectral results were compared with data from the independently synthesized products of **8** (Padwa *et al.,* 1983; Jutta et *al.,* 1999) and **9** (Wayne et *al.,* 1974; Anke et *al.,* 1985).

Although there is no properly identified products (due to shortage of research time) from the thermal decomposition of **3c** in dibromobenzene, data from the mass and ^{1}H NMR suggested that an alkene product similar to the one shown in Figure 40 could potentially be formed via a concerted type of mechanism.

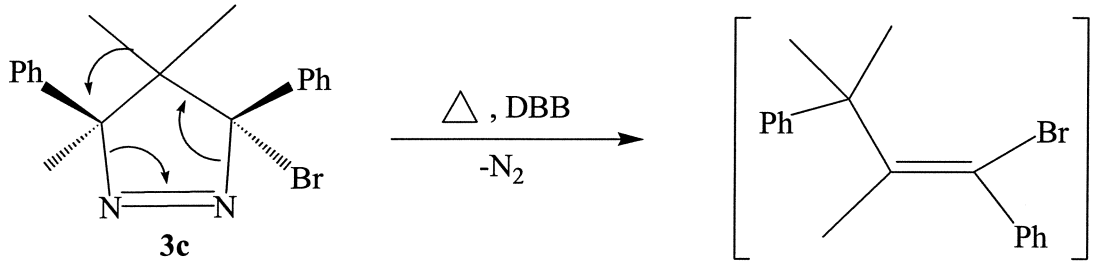


Figure 40. A suggested product and mechanism in the formation of olefinic product upon thermolysis of **3c** in DBB solvent.

Several possible pathways were considered as a means to justify the formation of **8** and **9** from the thermal decomposition of **3b**. However, based on a reported mechanism by Yoshiko (1989) and based on data collected from our kinetic and product studies, a general mechanism was proposed. It was suggested that halogenated cyclopropane product was first formed via a radical pathway. Then the cleavage of chlorine from the cyclopropane intermediate via an ionic pathway resulted in a carbocation, which was rearranged quickly to **8** and its olefinic isomers. This intermediate product was then converted into final product **9** in the presence of an acid (HCl) (Figure 41). The transformation of **8** to **9** was stagnant when there is still quinoline in the solution. This is because quinoline neutralized the HCl acid (a co-product during thermal decomposition of **3b**) that was necessary for the conversion of **8** to the end product **9**.

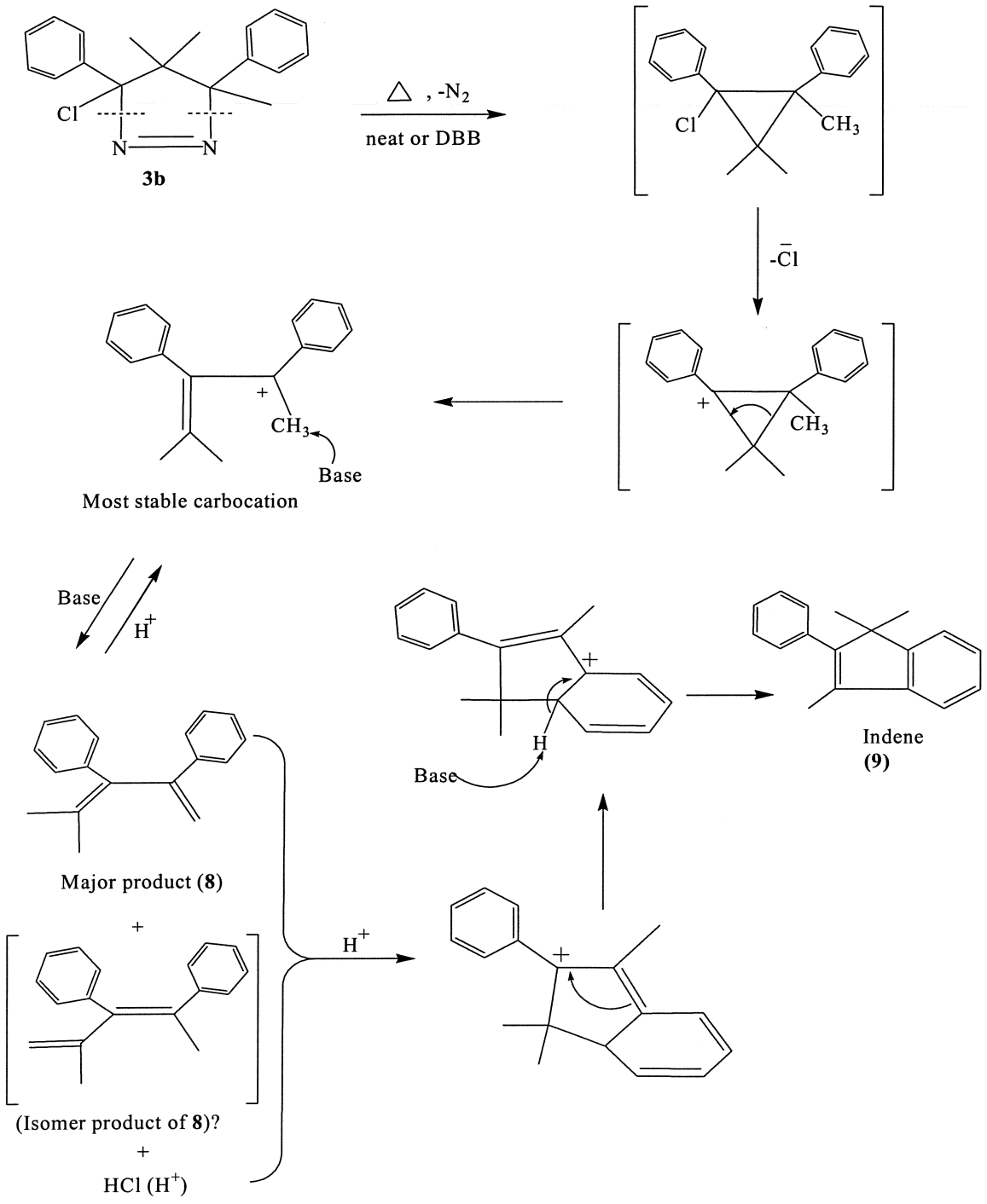
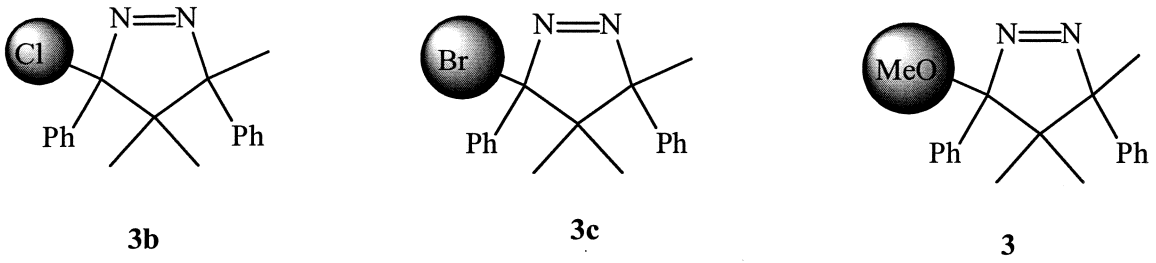


Figure 41. Proposed mechanism to the formation of **8** and **9** from the thermal decomposition of **3b** neat or in a non-polar solvent (DBB).

3.3 Factors that determine the outcome of products in the thermolysis of pyrazolines(3b-c).

One of several factors that determine the stereochemistry as well as the type of product from the thermally decomposed pyrazolines is the nature of substitutent on a pyrazoline ring such as electron donor or electron withdrawal groups. Pyrazolines, which are similar in geometrical structures, can yield different types of products upon thermolysis. As indicated on Figure 42, at C-3 position of all pyrazolines (**3, 3b, 3c**) there are electron-donating substituents. If the thermal decomposition of **3b** and **3c** undergoes a radical pathway of the C-N bond breakage, as it was evident for **3**, the electron deficient radical could have been formed at C-3 position and it would have been readily stabilized by the bromine atom rather than chlorine. This is because, relatively there is more electron density on the bromine atom that can easily be accessed or given to the neighboring electron deficient carbon.



3b **3c** **3**

Figure 42. All substituents at C-3 position of the pyrazoline are potential electron donors if decomposition was occurred via a radical pathway and can donate electrons to the neighboring electron deficient carbon.

Although we cannot draw direct relationship between thermal and photochemical reactions, due to significant difference of pathways of product formation, it is important to understand the process in photochemical reaction of azoalkanes or pyrazolines in order to draw a plausible explanation to some complex pathways in thermal reaction. A good example of photochemical reaction, which resembles to the observed products in our study is the photolysis

of α-chloroazoalkane. A previous report (Levi,1974) indicated that when the phenyl group is directly attached to the α-carbon atom, normal α-chloro azoalkane fragmentation (the fragmentation of C-N bond) became competitive with the C-Cl cleavage (Figure 43). Structure (A) on Figure 43 indicated the photolysis process of α-chloroazoalkane where the weaker C-N bonds break prior to the C-Cl bond. The structure (B) shows the photolysis of the αC-Cl bond in competition to that of the C-N bond.

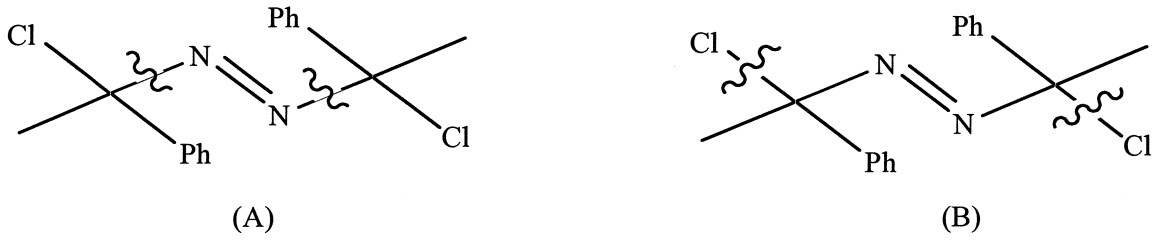


Figure 43. A photolysis of an azoalkane during a photochemical reaction.

3.4 Thermolysis of 3b-c in protic solvents.

Results from the product study for the thermolysis of **3b-c** in protic solvent were found to be extremely important because it provided new general method for the synthesis of 3-alkoxy-4,5-dihydro-3H-pyrazoles which is both safe and efficient. The thermal decomposition of **3b** in dry methanol and ethanol (protic solvents) resulted in the formation of **3** and 3-ethoxy-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole **(3d)** respectively via an ionic pathway (S_N1-type reaction). The breakage of the C-Cl bond prior to the C-N bond of **3b** could be facilitated by a hydrogen bonding between the methoxy group of the methanol, and the chlorine atom, which in effect weakens the C-Cl bond of the pyrazoline and eventually led to its cleavage (Figure 44). We observed that the thermolsysis of **3b** in methanol and ethanol occurred via the cleavage of the C-Cl bond in ionic pathway, instead of the normally expected radical cleavage of its C-N bond. Therefore, the thermolysis process of **3b** and **3c** in protic solvent found to be an

important discovery that pave a new synthetic method for future production of 3-alkoxy-3, 4-dihydro-3H-pyrazoles.

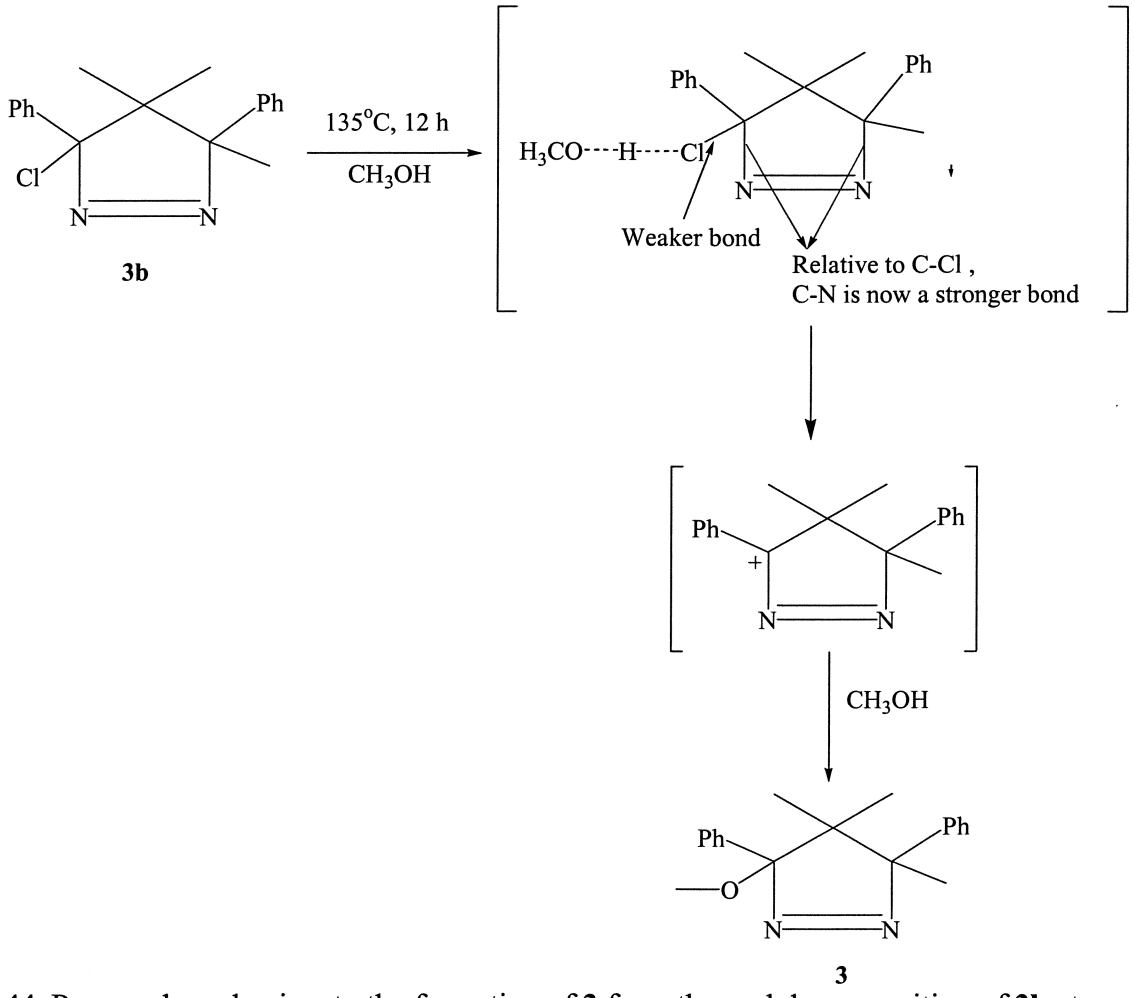


Figure 44. Proposed mechanism to the formation of **3** from thermal decomposition of **3b** at 135°C.

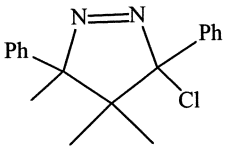
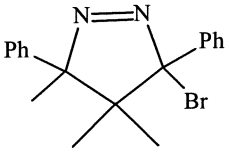
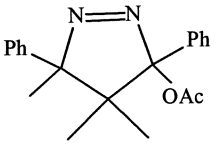
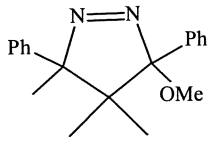
Unlike the product in methanol (protic solvent), the thermal decomposition of **3b** in aprotic solvent such as DBB or DCB resulted in olefinic products. This indicated that solvent polarity has direct effect on the outcome of products during thermolysis of **3b**.

3.5 Activation parameters from the thermal decomposition of 3b-c.

In the past, the study of the thermal decomposition of **3** in DCB provided the enthalpy of activation value of $\Delta H^{\ddagger} = 32.7 \pm 0.6$ (Vasquez et *al.*, 2000), and a radical pathway was suggested in the formation of a final product **5b**. Likewise, the change of enthalpy of activations ($\Delta H^{\ddagger}$) calculated for **3b** and **3c** in this experiment are 32.9±1 kcal/mol and 29.5±0.2 kcal/mol respectively and are in close agreement with the value reported for **3** (Vasquez et *al.*, 2000). Therefore, it is suggested that the thermolysis of both **3b** and **3c** in DBB may exhibit similar pattern of decomposition as **3** in DBB where the cleavage of the C-N bonds occurred in a radical pathways prior to the cleavage of the C-Cl or C-Br bonds. Therefore, it is viable that in a non-polar solvent (DBB), the breakage of C-N bonds of **3b-c** occurred via a radical pathway followed by the breakage of C-Br or C-Cl bonds in ionic pathways.

The activation parameters of **3b-c** were compared among similar compounds such as **3**,**3a**, and **3aa** (Vasquez et *al.*, 2000) and results are summarized in Table 6. Compounds **3b-c**, **3aa** and **3** are almost identical in structure. However, the nature of substituents at C-3 position of **3b-c** and **3** are expected to be very similar than that of **3aa**. This is because **3aa** has an electron withdrawing (acetoxy) substituent at αC-3 position while **3b-c** and **3** contained an electron donating halogen and methoxy groups respectively. Therefore, **3b-c** and **3** were expected to show almost similar values of activation parameters than that of **3aa.** The heat of enthalpy or entropy of activation value of **3, 3aa** (Vasquez et *al.*, 2000), **3c** and **3b** are summarized in Table 6.

Table 6. Summary of rate constants and kinetic parameters, and comparison of activation parameters among similar compounds **(3b, 3c, 3aa, and 3).**

Compd.	Structure	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	$\Delta G^{\ddagger}$(150°C) (kcal/mol)	$k_1 s^{-1} \times 10^{-5}$ (150 °C)
3b		32.9 ± 1.0	-2.4±0.07	33.9	7.3 ± 0.04
3c		29.5 ± 0.7	-6.9±0.03	32.43	42 ± 1.0
3aa		33.5 ± 1.0*	0.2 *	33.5*	17 ± 0.1 *
3		32.7 ± 0.6*	-1.8 *	33.5 *	12 ± 0.02 *

* (Vasquez et *al.*, 2000).

Enthalpy values for **3b** and **3c** in Table 6 varied by ±4kcal/mol and this difference is usually considered to be insignificant. Compound **3c** has the lowest activation energy value E_a (30.4kcal/mol) than that of **3b** and **3**. This is indicative of a successful transformation of **3c** to the transition state with less of an energy barrier. More negative value of entropy for **3b** and **3c** indicated that the compound lost their degree of freedom when going to the transition state. The entropy value of **3c** is –6.9±0.03eu while **3b** and **3** are –2.4±0.07eu and –1.8eu respectively. It is usually difficult to give a meaningful interpretation of entropy values that only differ by less than ± 10eu. In general, the negative values of entropy for the thermal decomposition of **3b-c** were

indicative of the higher state of disorder of molecules at the transition state. The free energy of activation ($\Delta G^{\ddagger}$) is the energy difference between reactants and transition state, and in our study it does not tell any different story than what was stated by $\Delta H^{\ddagger}$. The relationship between rate constant and $\Delta G^{\ddagger}$ is exponential, $k = k_0 e^{-\Delta G^{\ddagger}/RT}$ (k_0 and R are constants). For a small change in $\Delta G^{\ddagger}$ there is always a large change in rate constant value. Similarly, it was observed that for a slight difference in $\Delta G^{\ddagger}$ value between **3b** and **3c** (1.5kcal/mole), there were an approximately six fold difference in rate constant values between the two compounds.

CHAPTER IV

CONCLUSION

The starting materials (**3b-c**) were prepared successfully in order to carry out a kinetics study. A new compound of 4,4,5-trimethyl-3,5-diphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**4**) was isolated in 8% yield for the first time during a reaction procedure in the preparation of trans-3-chloro-4,4,5-trimethyl-3,5-diphenyl–3,4-dihydro-3H-pyrazole (**3b**), presumably via the N-hydrated intermediate. Compound **4** was also prepared in high yield (82%) during the reaction between lithium salt of 3,4,4-trimethyl-3,4-diphenyl-2H-pyrazole with TsF. The compound 3-bromo-4,4,5-trimethyl-3,5-diphenyl–3,4-dihydro-3H-pyrazole (**3c**) was synthesized in a reasonable yield (29%). An attempt toward the synthesis of **3c** using an NBS brominating agent resulted in significantly lower yield.

Thermal decomposition of **3b** provided essentially a single product that is indene (**9**) via a pentadiene intermediate **8.** Thermolysis of **3b** and its formation of **8** and **9** involved both radical and ionic pathways. The spectral data for the thermolysis of **3b** neat, in DBB or DCB solvents indicated that a bond between C-3 and N or C-5 and N was cleaved in a radical pathway prior to the ionic cleavage of C-Cl bond. The same analysis was applied in the cleavage of bonds for the thermolysis of **3c**. We have not done a group additivity calculation to determine which bonds of the C-N bonds were breaking first because there was no conclusive evidence to the formation of halogenated cyclopropane (since no cyclopropane product was isolated and characterized). However, it is speculated that either the C-3 and N bond breaks prior to the C-5 and N bond or both bonds (C-3-N, and C-5-N) could brake simultaneously. Thermal decomposition of **3b** in methanol and ethanol resulted in a substitution reaction where **3** and **3d** were produced in excellent yields. In protic solvents, it was proven that the C-X (X= Cl,Br) bonds of **3b** and **3c** are

the ones that breaks faster than the normally weaker C-N bonds via an S_N1-type of reaction. In contrary, thermal decomposition of **3b** in DBB (non-polar) solvent resulted in **8** and **9** where the cleavage of C-N bond came prior to the cleavage of C-X(Cl,Br). This observation led into a conclusion that thermal decomposition of **3b-c** under different polarities of solvents (protic vs. non-polar) resulted in different type of products. Therefore, the polarity of solvents play significant role in the thermolysis process of pyrazolines and their products. Most importantly, a product study for the thermal decomposition of **3b-c** under protic solvent showed that it is possible to synthesize other series of alkoxy-3H-pyrazoles with minimum cost and with out a need to deal with extraneous procedural steps.

The first order rate constant values that were determined for the thermolysis of **3b-c** indicated that **3c** is comparatively faster than **3b**. Compound **3c** has a slightly lower value of $\Delta H^{\ddagger}$ than that of **3b**. This indicated that the energy required to transform **3c** into the transition state is smaller than that of **3b**. It is difficult to interpret close values of $\Delta S^{\ddagger}$ especially after considering the corresponding error values; however, the negative $\Delta S^{\ddagger}$ values are representative of the magnitude of disorder at the transition state.The energy required for bond reorganization to form the activation complex is lower for **3c** therefore it was reasonable to expect faster rate of thermal decomposition for **3c** than **3b**.

CHAPTER V

EXPERIMENTAL SECTION

All starting compounds were commercially available and of reagent grade. However, p-toluenesulfonyl bromide (**6**) was prepared in our lab by modifying a procedure (Truce et *al.*, 1974), initially designed in the making of p-toluenesulfonyl iodide (**7**). The ACS grade chemicals were used in this experiment and all chemicals were supplied from Fisher Scientific, Acros, or Aldrich Co. Air and moisture-sensitive reactions were carried out in an oven-dried glasswares that were assembled hot and cooled in a stream of high purity argon. The synthesis of all compounds was verified by data collected from ^{1}H, ^{13}C NMR spectra using the Varian 60,VXR-300 and VXR-400 spectrometers. The chemical shift (δ) data are reported in ppm relative to TMS. Splitting patterns are referenced as s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. Rate of thermal decomposition were monitored using the Varian 60MHz spectrometer. The IR spectra were recorded on a Perkin Elmer Paragon 1710 FTIR spectrometer. The GC-MS data were recorded on a Shimadzu QP-500 mass spectrometer coupled to a Shimadzu GC-17A gas chromatograph. The melting point was measured using the Thomas Hoover Uni-melt apparatus and were calibrated with a standard solid. Elemental analysis and mass data were obtained at the Georgia State University on a Perkin Elmer Series 2400 analyzer.

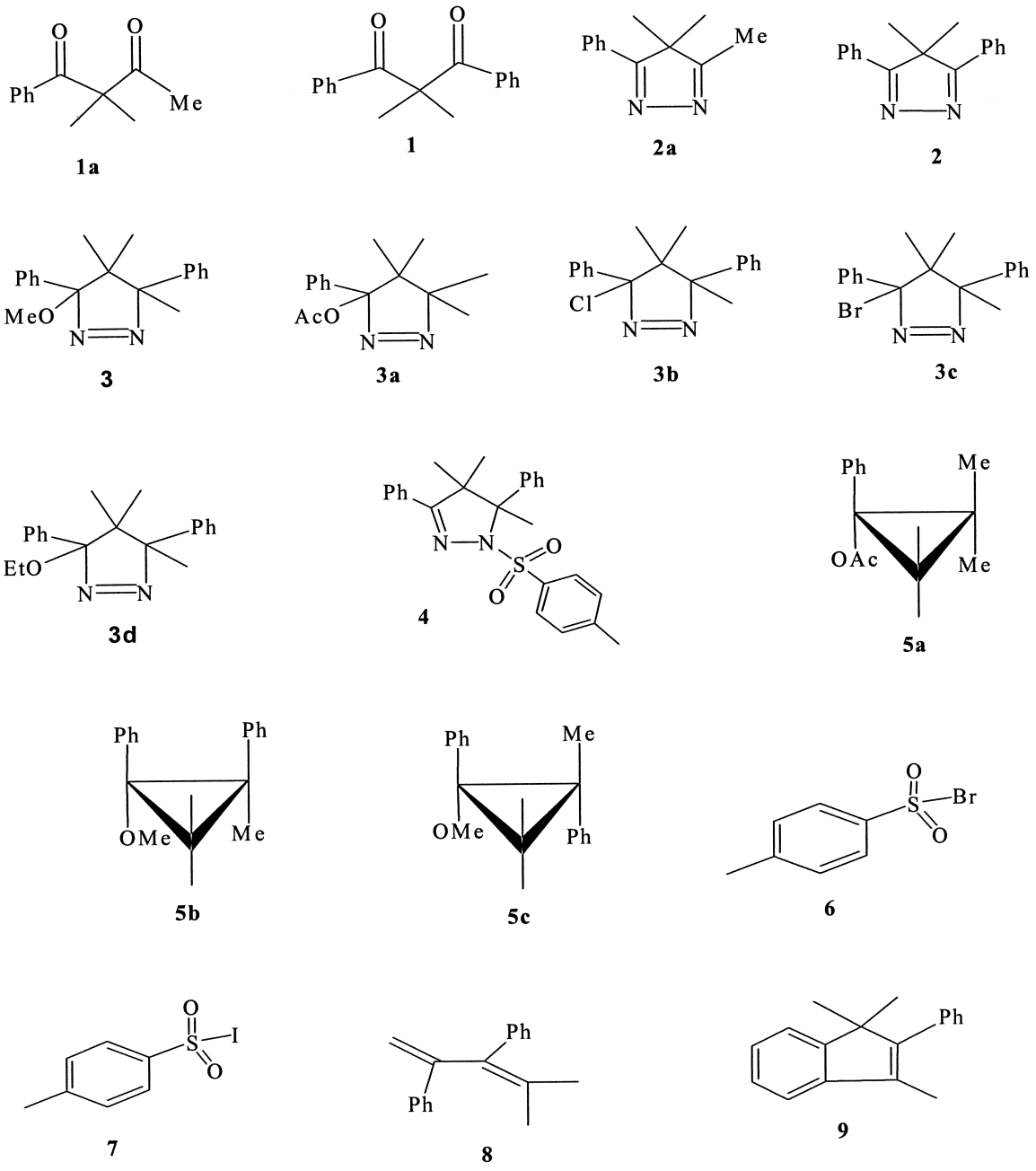
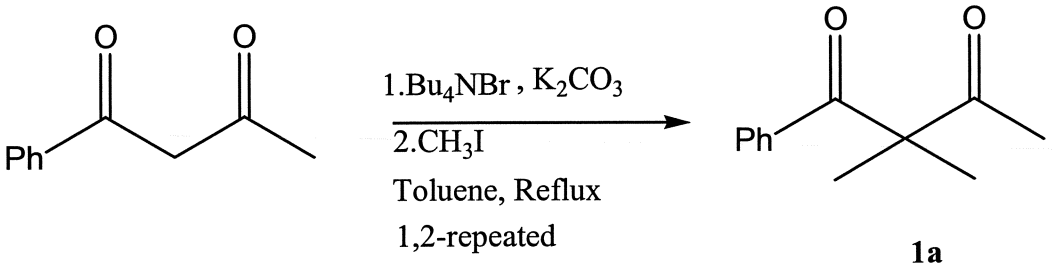


Figure 45. Overview of synthesized/ prepared products and their reference numbers.

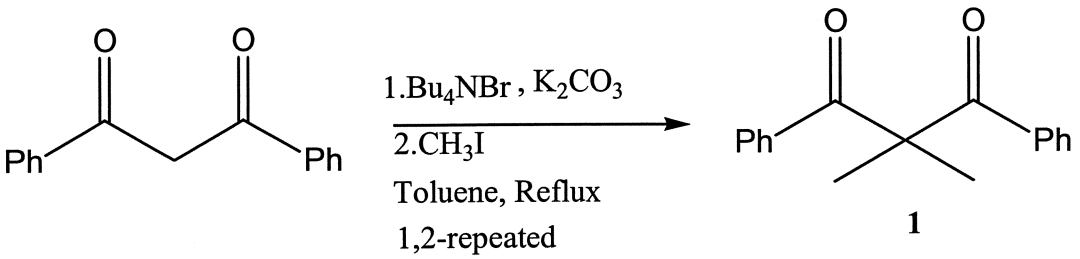


1a

Preparation of 2,2-dimethyl-1-phenyl-butane-1,3-dione (1a)

The following method for the synthesis of compound **1a** has been previously reported (Choudhary, et *al.,* 1989). In a dried and nitrogen purged 500 ml three-necked, round bottom flask equipped with a Dean-Stark trap and stir bar, was placed 1-benzoylacetone (5 g, 0.031mole), toluene (150ml), anhydrous powdered potassium carbonate (12.3 g, 0.090mole), and anhydrous tetra butyl ammonium bromide (Bu_4NBr) (0.36 g, 0.001 mole). The solution mixture was stirred vigorously under reflux for 3h under positive pressure of nitrogen. The mixture was cooled to room temperature and methyl iodide (8 ml, 0.056 mole) was added within a period of 15 min with the help of a dried glass syringe. After stirring a mixture for an additional 1h at room temperature, a completion of the monoalkylation was monitored on a TLC plate. Then a second portion of anhydrous potassium carbonate (6.15 g, 0.045mole), Bu_4NBr (0.36 g, 0.001 mole) were added at once and refluxed for overnight (10 h). After cooled to an approximately to room temperature (below 40 ^{0}C), the second portion of methyliodide (3.5 ml, 0.025 mole) was added drop wise. After stirring the solution mixture for additional 30 min, the mixture was heated under reflux for additional 1h. After cooling the solution to room temperature, the inorganic salt was removed by a suction filter and washed with diethyl ether (33 ml). The solution was also washed with water (3X,10ml), dried with anhydrous magnesium sulfate and concentrated by a rotary evaporator. The crude product **1a** was recrystallized from hexane to yield 5.5 g (93 %) of solid **1a**, mp 81-83°C, Lit mp = (81-83°C)(Choudhary, et *al.,* 1989) ^{1}H

NMR ($CDCl_3$); δ1.4(s, 6H), 2.1 (s, 3H) 7.2-7.6 (m, 3H), 7.75-7.9 (m, 2H). Lit. ^1H NMR (CDCl3); 1.48 (s, 6H), 2.09 (s, 3H), 7.4-7.53 (M, 3H), 7.78-7.83 (m,2H).

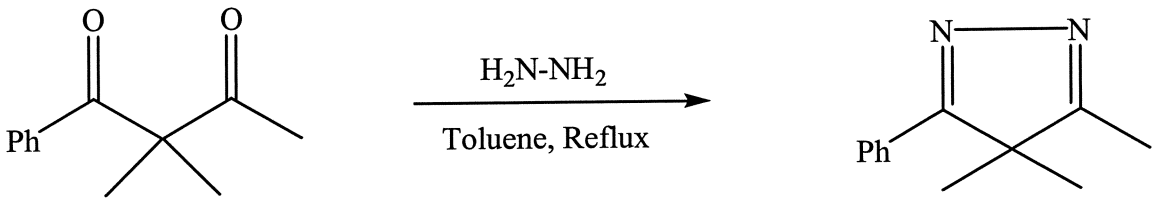


1

Preparation of 2,2-dimethyl-1,3-diphenyl-1,3-propanedione (1)

The following method for the synthesis of compound **1** has been previously reported (Choudhary, et *al.,* 1989). In a dried and nitrogen purged 500 ml three-necked round bottom flask equipped with a Dean-Stark trap and stir bar was placed dibenzoylmethane (10 g, 0.045 mole), toluene (270 ml), anhydrous powdered potassium carbonate (25g, 0.18 mole), and Bu_4NBr (1.0 g, 0.003 mole). The solution mixture was stirred vigorously under reflux for 3h under positive pressure of nitrogen. The mixture was cooled to room temperature and methyliodide (25 ml, 0.176 mole) was added within a period of 15 min with the help of a dried glass syringe and allowed to stir for 30min. A second portion of anhydrous powdered potassium carbonate (30 g, 0.217 mole) and Bu_4NBr (1.6 g, 0.005 mole) all added at once and refluxed for overnight (10 h). After cooled to room temperature (below 40 ^0C), the second portion of methyliodide (25 ml, 0.176 mole) was added over a period of 30 min. After stirring the solution mixture for additional 30 min, the mixture was heated under reflux for additional 1h. After cooling the solution to room temperature, the inorganic salt was removed by a suction filter and washed with diethyl ether (100 ml). The solution then washed with water (3X, 15ml) and dried

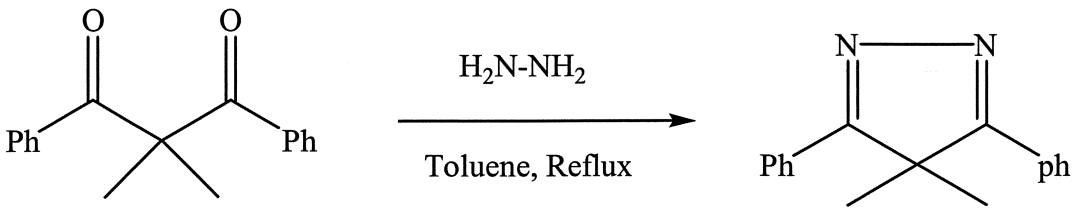
with anhydrous magnesium sulfate and concentrated by a rotary evaporator. The crude product of **1b** was recrystallized from hexane to yield 10.67 g of white solid (94 %), mp 95-96°C (95-96°C (Choudhary, et *al.*, 1989)); ^{1}H NMR ($CDCl_3$); δ1.72(s, 6H), 7.32-7.46 (m, 6H), 7.87-7.91(m, 4H); MS: M +/e 252; IR (neat) 1682cm^{-1}, 1676 cm^{-1}.



1a **2a**

Preparation of 4,4-dimethyl-3-phenyl-5-methyl-4H-pyrazole (2a)

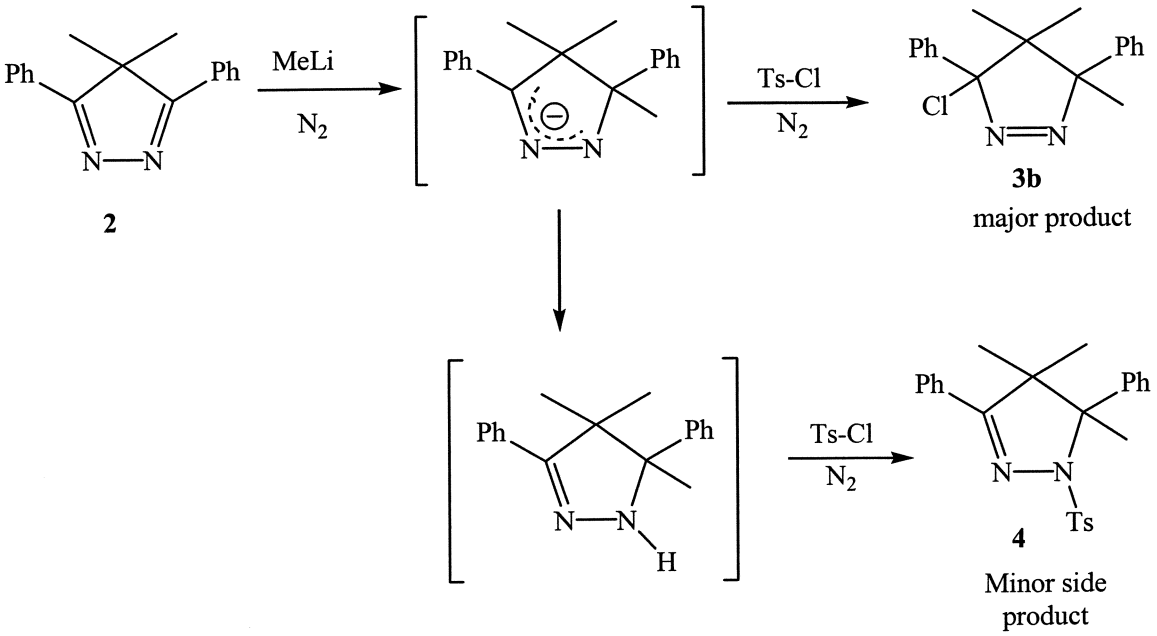
Compound **2a** were prepared by the reaction of **1a** with hydrazine. The following procedure represents the preparation method by Baumstark, *et al.* (1990). In a dried and nitrogen flushed three neck round bottom flask equipped with Dean-Stark trap and a stir bar, **1a** (10 g, 0.053 mole), p-toluenesulfonic acid monohydrate (0.5 g, 0.003 mole), Toluene (240 ml) and Hydrazine (4 ml, 0.125 mole) was added under neutral atmosphere (argon). The mixture was heated under reflux (under a positive pressure of argon gas), and the water was removed using a Dean-Stark trap. After cooling the solution to room temperature, the mixture was washed with 5% $NaHCO_3$ (20 ml, 3X) and the organic layer was separated and dried with anhydrous magnesium sulfate. The volatile components were removed under reduced pressure giving a red colored crude solid product. The solid was then recrystallized from hexane to give a pure light red dry solid product **2a** (7.69 g, 0.041 mole) in a 92 % yield, mp 94-95 (Lit.mp 94-95 °C (Baumstark, et *al.*,1990)). ^{1}H NMR ($CDCl_3$): δ1.40 (s, 6H), 2.22 (s, 3H), 7.4-8.4 (m, 10 H). IR (KBr): 2875-3100cm^{-1} (C-H).



1 **2**

Preparation of 4,4-dimethyl-3,5-diphenyl-4H-pyrazole (2)

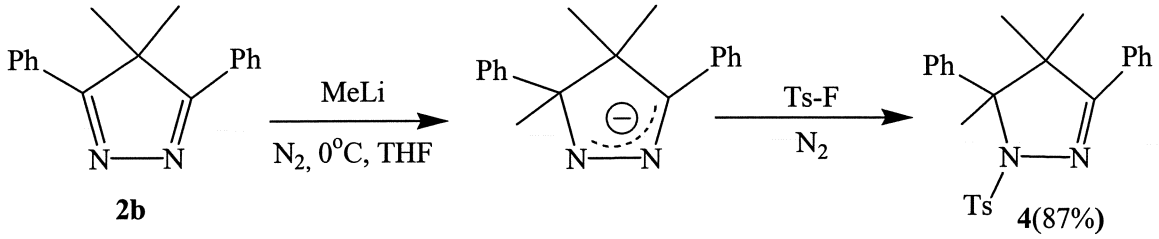
Compound **2** were prepared by the reaction of the corresponding 4,4-dimethyl-1,3-diphenyl-1,3-propanedione **1** with an hydrazine. The following procedure is representative for the preparation of **2** (Baumstark, et *al.,* 1990). In a dried and nitrogen flushed three neck round bottom flask equipped with a Dean-Stark trap and stir bar, 2,2-Dimethyl-1,3-biphenyl-1,3-propanedione **1** (8 g, 0.032 mole), p-toluenesulfonic acid monohydrate (0.5 g, 0.003 mole), toluene (240 ml) and Hydrazine (4 ml , 0.122 mole) were added all at once under neutral condition. The mixture was heated under reflux for 2-3 h and water was periodically removed from the Dean-Stark trap. After the solution cooled to room temperature, it was washed with 5 % $NaHCO_3$ (20 ml, 3X). An organic component of the product was dried with anhydrous magnesium sulfate. The volatile components were removed under reduced pressure. The crude solid was recrystalized from hexane to give a pure white solid **2** (7.7 g, 0.031 mole) in 97 % yield, mp 126-127° (lit mp = 127-128 ° C (Baumstark et *al.*, 1990)). ^{1}H NMR ($CDCl_3$): δ1.7 (s, 6H), 7.4-8.4 (m, 10 H).



Preparation of trans-3-chloro-4,4,5-trimethyl-3,5-diphenyl–3,4-dihydro-3H- pyrazole (3b) and isolation of 4,4,5-trimethyl-3,5-diphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole(4).

The following procedure is representative to the formation of **3b** (Kennedy et *al.,* 2004). In a pre-dried and nitrogen flushed three neck round bottom flask, 3,3-dimethyl, 2,4-diphenyl-4H-pyrazole (1.053 g, 0.004 mole), a stir bar and 50 ml of dry THF was added. Once the solid is dissolved, the system was cooled to 0°C using a salt-ice bath. After 5 min of stirring, 1.6 M methyllithium (4.0 ml (1.6eq), 0.003 mole) were added using dry glass syringe. The solution turned dark immediately upon addition of the methyllithium. Then it was stirred for 2h in a salt-ice bath (0°C) followed by addition of p-toluenesulfonylchloride (1.004 g, 0.0053 mole) that

was dissolved in 20 ml of dry THF under argon gas. The mixture was stirred for additional 1h followed by the addition of 20 ml of degassed and saturated ammonium chloride via a plastic syringe. The solution was stirred for additional 20 min and the organic layer was separated and washed with saturated sodium bicarbonate (3X, 10 ml). The organic layer was then dried with anhydrous magnesium sulfate. After separating the $MgSO_4$ using a gravity filtration, pressure vaporization of the solvent led to the recovery of the brownish solid crude product. Further purification of this crude product using chromatotron (200 mg at a time) (100% petroleum ether was used as a mobile phase in the beginning followed by increase in polarity to 95:5 v/v of pet-ether and ethyl acetate mixture) resulted in a separation of two compounds. The first eluted fraction was **3b** and the second fraction was identified as 4,4,5-Trimethyl-3,5-diphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole(**4**). Pure white solid **3b** (1.1 g, 3.7mmole) has been isolated in 91 % yield. m.p 122-123 ^{0}C (Lit.mp. 123.5-124.5 (Kennedy et *al.,* 2004); IR (KBr pellet), 700-755 (C-Cl, Strong), 2940-2980 (C-H), 3001-3067 (C=C-H), 1445-1600 (aromatic (phenyl)), ^{1}H NMR (deuteriochloroform): δ -0.154 (s,3H), 1.59 (s,3H), 1.82 (s, 3H), 7.3-7.4 (m, 8H), 7.5-7.61 (m,2H); ^{13}C NMR ($CDCl_3$): δ 20.3, 22.0, 27.1, 46.0, 97.8, 108.4, 124.6,125.8, 127.4, 128.1, 128.3, 128.7, 139.4, 142.2. MS: M^+/e = 264 (104 base), Cl-266 (M^+ + 2). A pure white solid of **4** (135g, 0.32 mmoles) was also isolated in 8% yield. m.p 169-171 ^{0} C, IR (KBr pellet) 1333 (Asymmetric $S(=O)_2$ stretch), 1154 (Symmetric $S(=O)_2$ stretch), 1030-1230 (C-N). ^{1}H NMR (deuteriochloroform): δ 0.78 (s, 3H), 1.26 (s, 3H), 1.72 (s, 3H), 2.42 (s, 3H), 7.26-7.91 (m,14H); ^{13}C NMR (deuteriochloroform): δ 18.82, 19.87, 20.72, 23.0, 55.2, 80.1, 126.4, 127.1, 127.2, 127.3, 127.6, 128.4, 129.2, 129.5, 130.8, 137.1, 139.6, 143.6, 161.0. MS: M^+/e = 418 (263 base), S-419 (M^+ + 1). Anal. Calcd. $C_{25}H_{26}N_2SO_2$: C, 71.8; H, 6.22; N, 6.69. Found: C, 71.68; H, 6.21; N, 6.68.

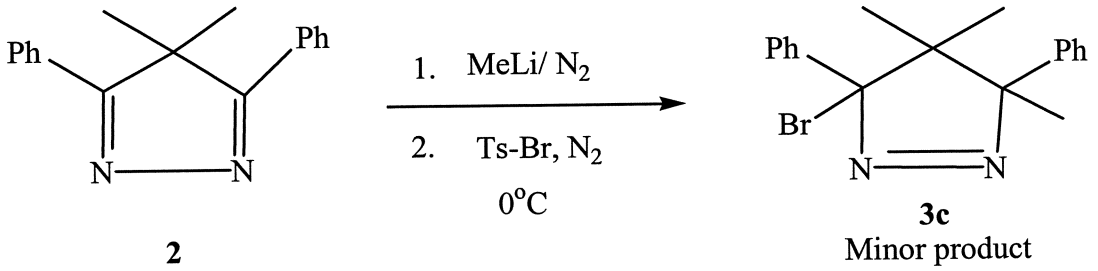


Synthesisof 4,4,5-trimethyl-3,5-diphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole(4).

Compound **4** was previously isolated in minor yield during the preparation of **3b**. The synthesis of **4** in minor yield led to an experiment, which resulted in the production of **4** in good yield. Procedure used in the preparation of **3b** and isolation of **4** was representative for an independently synthesized product **4** using Ts-F as a tosylating agent.

In a pre-dried and nitrogen flushed three neck round bottom flask, 3,3-dimethyl, 2,4-diphenyl-4H-pyrazole (1.053 g, 0.004 mole), a stir bar and 50 ml of dry THF was added. Once the solid is dissolved, the system was cooled to 0°C (using a salt-ice bath). After 5 min of stirring, 1.6 M methyllithium (4.0 ml (1.6eq), 0.003 mole) was added using a dry glass syringe. The solution turned dark immediately upon addition of the methyllithium. The solution was then stirred for 2h at 0°C. p-toluenesulfonylfuloride (1.0 g, 0.0057 mole) dissolved in 20 ml of dry THF, was then added in the reaction mixture under neutral condition. The mixture was stirred for additional 1h and a 20 ml of degassed and saturated ammonium chloride was added through a plastic syringe and the solution was stirred for additional 20 min. The organic layer was then separated and washed with saturated sodium bicarbonate (3X, 10 ml). The organic layer was then separated and dried with anhydrous magnesium sulfate. After gravity filtration and vaporization of the solvent under reduced pressure, the light yellowish solid was collected as a crude product. Further purification of this crude solid by recrystallization with voluminous absolute ethanol resulted in the production of pure white needle like solid **4** in 82% yield. m.p169-171 ^{0} C, IR

(KBr pellet) 1333 (Asymmetric $S(=O)_2$ stretch), 1154 (Symmetric $S(=O)_2$ stretch), 1030-1230 (C-N). ^1H NMR (deuteriochloroform): δ 0.78 (s, 3H), 1.26 (s, 3H), 1.72 (s, 3H), 2.42 (s, 3H), 7.26-7.91 (m, 14H); ^{13}C NMR (deuteriochloroform): δ 18.82, 19.87, 20.72, 23.0, 55.2, 80.1, 126.4, 127.1, 127.2, 127.3, 127.6, 128.4, 129.2, 129.5, 130.8, 137.1, 139.6, 143.6, 161.0. MS: $M^+/e = 418$ (263 base), S-419 ($M^+ + 1$).



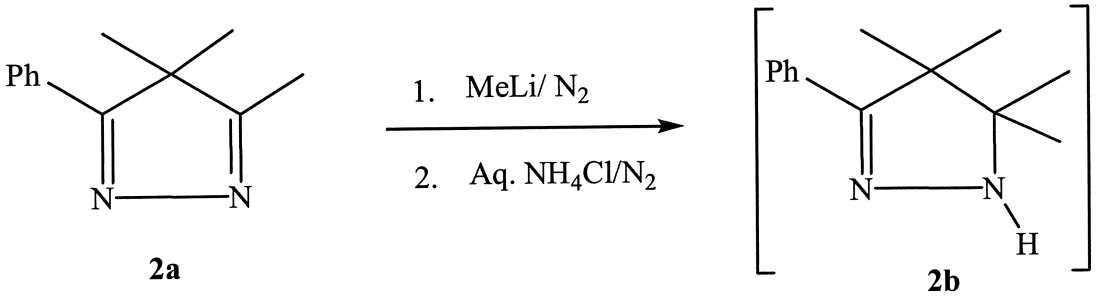
2

3c
Minor product

Synthesis of 3-bromo-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (3c).

3c was synthesized in our lab with a very small percent yield using an NBS brominating agent. The following procedure is representative for the synthesis of **3c** in good product yield. In a pre-dried and nitrogen (N_2) purged round bottom flask, pure compound **2** (1g, 4.03 mmole), a stir bar and dried tetrahydrofuran (THF, 50 ml) were added at once and stirred for 10 min. The reaction was cooled to 0 ^0C (in a salt- ice bath). After stirring the solution for additional 5 min, 1.6 equivalent of 1.6 M methyllithium (4 ml, 6.45 mmole) was added using a dried glass syringe. The solution was stirred for 1h at 0°C and 2.5eq.of p-toluenesulfonyl bromide (2.37 g, 10.07 mmole), dissolved in 15 ml of dried THF was transferred into the reaction mixture using a dried glass syringe. The solution was stirred for 1h at 0°C and a degassed saturated aqueous ammonium chloride solution (20 ml) was added. After 15 min of additional stirring, the solution was washed three times with saturated aqueous sodium bicarbonate (15ml) and dried with anhydrous magnesium sulfate. Filtration and evaporation of the solvent at room temperature

gave a light yellow solid identified as a crude product of **3c.** Addition of an absolute ethanol into a crude solid resulted in the precipitation of white crystals, which gave ^{1}H NMR signals with six equal heights. This compound is not characterized completely and not identified as a product yet. However, the filtrate was then concentrated in a rotary evaporator (in a 100 ml pear shaped flask) and a viscous liquid was obtained. Addition of another portion of absolute ethanol (200% proof pure ethanol) with the help of a pipette resulted in the precipitation of another batch of white crystals that was filtered off and identified as pure compound of **3c** (200 mg). The filtrate was again concentrated in a rotary evaporator for the third time and another portion of absolute ethanol was added giving of another white solid **3c** (160 mg). In overall, the pure amount of **3c** (360 mg, 0.00105 mole) was collected in 26% yield. M.p. 146-147 °C; IR (KBr pellet), (C-Br, Strong), 2940-2980 (C-H), 3001-3067 (C=H), 1445-1600 (aromatic (phenyl)), ^{1}H NMR (deuteriochloroform): δ (s, 3H), (s, 3H), (s, 3H), (m,10H); ^{13}C NMR ($CDCl_3$): δ 20.2, 23.3, 26.5, 46.5, 97.7, 105.2, 125.3,126.2, 127.5, 128.2, 128.4, 128.7, 140.8, 143.0. MS: M^{+}/e = 343.2 (264.2 base), 345.2 (M^{+} + 2). Anal. Calcd. For: $C_{18}H_{19}ClN_2$: C, 62.98 ; H, 5.58 ; N, 8.16 . Found: C, 63.06; H, 5.67 ; N, 7.44.

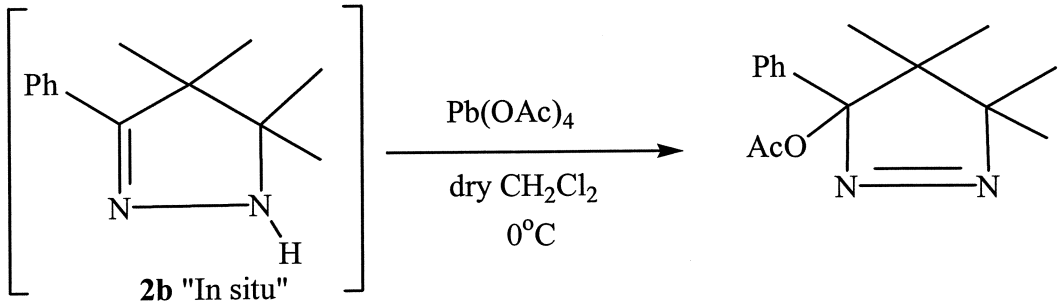


2a **2b**

Preparation of 4,4,5,5-tetramethyl-3-phenyl-4,4-dihydro-1H-pyrazole.

The preparation, isolation, purification and storage of these compounds were carried out under inert atmosphere. The synthesis of this compound has previously been reported (Baumstark, et

al., 1987). The following preparation procedure is representative. A solution of 4,4,5-trimethyl-3-phenyl-4H-pyrazole (2.4g, 0.013 mole) dissolved in anhydrous THF was transferred into 500 ml flask under inert atmosphere. The solution was then cooled to 0°C and 1.1 equivalence of 1.6M methyllithium (9 ml, 0.014 mole) in cyclohexane-ether (70:30) was added to the reaction mixture via dried glass syringe. The solution immediately became dark after addition of methyllithum. After stirring the solution at room temperature for 30 min, the reaction mixture was quenched with excess of saturated ammonium chloride solution at –78 °C. The solution was then allowed to warm to room temperature. The organic layer was separated, washed with brine and dried over anhydrous magnesium sulfate. The crude oil of **2b** *in situ*, 80% yield (2.1 g, 10.4mmole) was dissolved in dry dichloromethane under nitrogen and was used in the next step with out characterization.

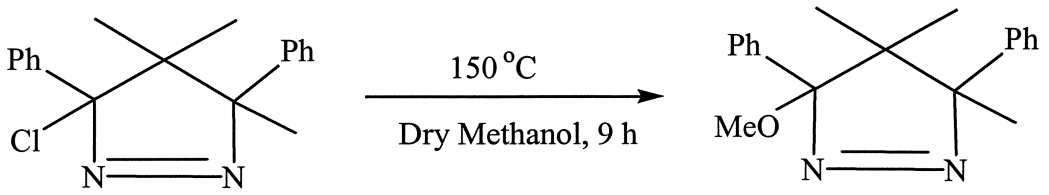


2b "In situ"

Preparation of 3-acetoxy-4,4,5,5-tetramethyl-3-phenyl-4,5-dihydro-3H-pyrazole. (3a)

The following procedure is representative to the preparation of **3a** (Kennedy *et al.,* 1991). A clean 500ml, three necked round bottomed flask equipped with a magnetic stirring bar and pressure equalizer funnel was purged with nitrogen. Then 4,4,5-tetramethyl-3-phenyl-4,5-dihydro-1H-pyrazole (2.1 g, 0.0104 mole) dissolved in 86 ml of dry dichloromethane was added drop wise into a 500 ml round bottom flask which contained lead (IV) acetate (0.93g, 2.1mmole) dissolved in 10 ml of dichloromethane. (**Caution**: lead is a dangerous metal and handling it

required extreme care). The reaction mixture was stirred at 0°C under totally anhydrous condition for 1h then allowed to warm to room temperature. The crude product was washed with 5% hydrochloric acid (2.5 ml), water, aqueous EDTA and brine. The organic layer was dried with magnesium sulfate and the solvent was removed under reduced pressure. The crude product (1.4 g, 0.005 mole) was purified by column chromatography using 5% acetone and 95% hexane mobile phase giving a yellowish pure solid (50 mg, 0.19mmole) in 2 % yield. M.P= 101-103 (lit. mp = 102-104 (Kennedy *et al.,* 1991)); ^{1}H NMR ($CDCl_3$): δ 0.20 (s, 3H), 1.20 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 2.02 (s, 3H), 7.43 (m, 5H). Lit. ^{1}H NMR ($CDCl_3$): 0.20 (s, 3H), 1.17 (s, 3H), 1.45 (s, 3H), 2.02 (s, 3H), 7.43 (m, 5H).

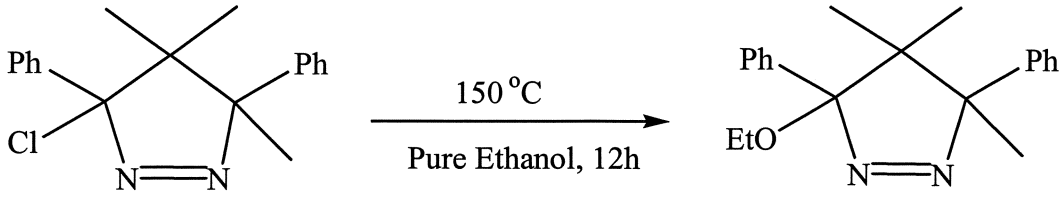


3b **3**

Preparation of 3-methoxy-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (3).

The synthesis of compound **3** was previously reported (Kennedy *et al.,* 1991). The following thermal decomposition procedure is a new alternative method for the preparation of **3** in higher yield. In a dried and argon flushed high-pressure tube, **3b** (50 mg, 0.17mmole), dried and distilled methanol (15ml) was added in a high pressure tube and the solution was bubbled with argon gas. The tube was then immediately screwed and tightly sealed before placed in preheated silicon oil bath at 135 ± 1°C. The solution mixture was allowed to reflux at 135 ± 1°C for 12 h. Removal of the solvent by reduced pressure resulted in crude solid product **3**. Further purification of the crude product by chromoatotron technique (using a mobile phase v/v 95% hexane: 5% ethyl acetate mixture) resulted in a pure product of **3** (40 mg, 0.136mmoles) in 80 %

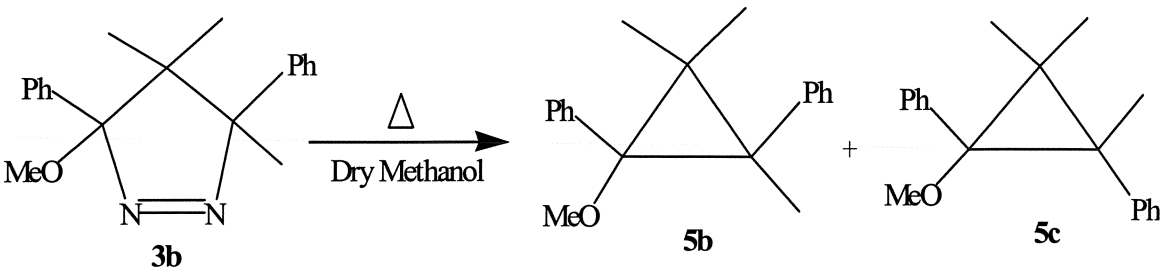
yield. mp = 98-99 (Lit. mp = 98-100, Lit. yield 22, 63% (Kennedy *et al.*, 1991)). ^{1}H NMR (300 MHZ, $CDCl_3$): δ -0.32 (s,3H), 1.28 (s, 3H), 1.73 (s, 3H), 3.38 (s, 3H), 7.25-7.49 (m, 10H). Lit. ^{1}H NMR ($CDCl_3$): -0.35 (s, 3H), 1.25 (s, 3H), 1.75 (s, 3H), 3.45 (s, 3H), 7.3 - 7.8 (m, 10H).



3b **3d**

Synthesis of 3-ethoxy-4, 4,5-trimethyl-3, 5-diphenyl-4,5-dihydro-3H-pyrazole (3d)

The following thermal decomposition procedure is representative to the synthesis of compound **3d** in higher yield. In a dried and argon flushed high pressure test tube, compound **3b** (100 mg, 0.335mmole), dried and distilled methanol (15ml) was added and the solution was bubbled with argon gas. The tube was then sealed and placed in preheated oil bath at 130 ± 2 °C for 12 h. Removal of the solvent by reduced pressure resulted in a mixture of crude solid and viscous liquid. Further purification of the crude product by the chromatotron, using hexane as a mobile phase, resulted in a pure solid product **3d** (70 mg, 0.23mmole) in 68 % yield. mp = 74-76 °C. ^{1}H NMR (300 MHZ, $CDCl_3$): δ -0.33 (s, 3H), 1.08-1.13 (t, 3H), 1.3 (s, 3H), 1.75 (s, 3H), 3.6-3.7 (m, 2H), 7.25-7.49 (m, 10H). MS: M^+/e = 309 (base), 310 (M^+ + 1), 311(M+2).



3b **5b** **5c**

Thermal decomposition of 3b in dry methanol at 150°C.

In a dried high pressure tube, **3b** (100mg, 0.335mmole) and distilled methanol (10 ml) were mixed and an argon gas was bubbled into the solution. The tube was then placed in a silicon oil bath at 150°C for 2 days. The solvent was then removed under reduced pressure giving a crude products of cis/trans-1-methoxy-2,3-trimethyl-1,3-diphenyl-cyclopropane (**5b-c**). Further purification of the crude product with chromatotron (using a 95:5 (pet-ether: ethyl acetate) mobile phase) resulted in isomeric products, **5b** and **5c,** that could not separate on a silica gel. Pure compounds of **5b-c** (90 mg, 0.34 mmole) were isolated in 97 % yield with a product ratio of 4:1 respectively based on ^{1}H NMR integration. ^{1}H NMR of **5b** (300 MHZ, $CDCl_3$): δ 0.90 (s, 3H), 1.40 (s, 3H), 1.5 (s, 3H), 3.25 (s, 3H),7.1-7.5 (m, 10H). Lit. (Kennedy et *al.,* 1991) ^{1}H NMR ($CDCl_3$): 1.01 (s, 3H), 1.42 (s, 3H), 1.54 (s, 3H), 3.23 (s, 3H), 7.15-7.35 (m, 10H); MS: 266 (M+), 251, 219, 204, 135, 105 (base), 91, 77,73. **5c**: δ 1.05 (s, 3H), 1.20 (s, 3H), 1.27 (s, 3H), 3.0 (s, 3H), 7.1-7.5 (m, 10H). MS: 266 (M+), 251, 219, 204, 135, 105 (base), 91, 77,73.

Applied procedure for the thermal decomposition of 3b-c.

The kinetic experiment was performed using the procedure (Vasquez et *al.,* 2000). A 25mg samples of pure compounds of the 3-halogenated-4,5-dihydro-3H-pyrazoles (either **3b** or **3c**) was weighed into 5mm NMR tubes followed by the addition of equal moles of 2-bromoanisole (internal standard) and 0.5 ml of 1,3-dibromobenzene (b.p=218-219°C) or 1,2-dichlorobenzene (n.d.=1.55). The NMR tube was cupped and sealed immediately. Then it was heated at a constant temperature in a silicon oil bath (T ± 1.0). A regular watch was used for timing. Timing was handled very carefully (the initial and ending time was recorded correctly). Thermolysis measurement at 150°C and 160°C was repeated to check the reproducibility of the method as well as the accuracy of the measurements.

Immediately after the tubes were removed from the hot silicon oil bath, it was placed in an ice bath to protect any further decomposition. The progress of the reaction was observed by monitoring the disappearance (^{1}H NMR electronic integration) of the most upfield methyl group signal of the 3H-pyrazole derivatives vs. that of the methoxy group of the 2-bromoanisole (internal standard). The discoloration of products was also observed. We found it very important to keep the NMR sample in the fridge before and after NMR analysis to protect pre or post decomposition by light or heat.

Neat solid thermal decomposition of trans-3-chloro-4,4,5-trimethyl-3,5-diphenyl–3,4-dihydro-3H-pyrazole (3b) .

A neat solid of **3b** (80 mg, 0.27mmoles) was allowed to stand in a sealed high-pressure tube at 150 °C for 22 h. After removal of the tube from a hot silicon oil bath, it was cooled in an ice bath. A purification by a chromatotron (petroleum ether was used as a mobile phase) resulted in a clear oil product which was identified as 2,3-diphenyl-4-methyl-1,3-pentadiene **(8)** (32 mg, 0.137mmoles) in 51% yield (This yield includes a non-separated isomeric products of **8**). The structure of the major product was proven based on comparing mass, IR and ^{1}H NMR data with that of the literature (Padwa et *al.,* 1983). IR (neat) 3100, 2900, 1600, 1440, 900cm^{-1}. ^{1} H NMR (300 MHz, Chloroform-d): σ 1.82 (s,3H), 1.84 (s,3H) 5.15(d,1H, *J*= 1.5Hz), 5.16(d,1H, *J*=1.5Hz), 6.93-7.44 (m, 10H) ; MS, m/e 234 (M^+, base), 219,115,77.

In another experiment a neat solid of **3b** (100 mg, 0.000335 mole) was heated in a hot silicon oil bath at 200 °C for about three days. Then, excess HCl gas was bubbled in the tube and the heating was continued for a day. The thermally decomposed crude product was purified by chromatotron using a 100 % hexane mobile phase. A pure product of 1,1,3-trimethyl-2-phenylindene **(9)** was obtained in 96 % yield (97 mg, 0.4mmoles) whose structure was later verified by both ^{1}H and ^{13}C NMR and compared with the literature (Anke *et al.,* 1985). ^{1} H NMR (300 MHz, Chloroform-d) σ 1.25 (s,6H), 2.1 (s,3H), 8.1(m, 5H) ; ^{13}C NMR ($CDCl_3$): δ , -0.02, 11.02, 24.3, 50.93, 119, 121.1, 125.1, 126.5, 126.9, 128.1, 129.4, 132.4, 137, 144, 151.8, 153; MS, m/e 234 (M^+), 219 (base),204,178,141,101.

Thermal decomposition of trans-3-chloro-4,4,5-Trimethyl-3,5-Diphenyl–3,4-dihydro-3H-pyrazole (3b) in 1,3-dibromobenzene solvent with or without the presence of a base.

In 5 mm NMR tube 25 mg of **3b**, 0.5 ml of 1,3-dibromobenzene and excess (three drops (~0.015 ml)) of quinoline was added together. In another tube, the same solution mixture as

above but with out the addition of quinoline was prepared. Both tubes were then capped and sealed and placed in a hot silicone oil bath (150°C). The decomposition process was then monitored by ^{1}H NMR spectrum by stopping the decomposition process at a randomly chosen time frame. As some point in the thermal decomposition process it was observed by the 1H NMR that there were a signal that indicated the formation of an intermediate product **8** and its isomers as a minor product. However, as the decomposition continues for a longer time in the same silicon oil bath, the tube that contained no quinoline showed signals on the ^{1}H NMR spectra, which is representative of the formation of (**9**). On the other hand, the tube which excess quinoline was added remain to show a signal for **8** and not for **9** no matter how longer it was heated at 150°C.

Formulas used to calculate rate constant values and activation parameters

The study of kinetics does not only deal with the rate and activation parameter calculations. It also provides information, which is needed to arrive to a plausible mechanism of a reaction. The type of reaction dealt in this kinetics experiment is unimolecular reaction. Therefore, the rate of the reaction is considered to be first order and was verified by a straight-line fit of the ln (k) vs. 1/T plot. The change in enthalpy ($\Delta H^{\ddagger}$) was calculated from the slope values of the ln (k/T) vs. 1/T plot (Eyring plot) multiplied by a gas constant value (R = 1.9872cal $Mole^{-1}K^{-1}$). The $\Delta H^{\ddagger}$ value (almost same as E_a under same solvent condition and constant pressure) was used in the calculation of $\Delta G^{\ddagger}$ and $\Delta S^{\ddagger}$ parameters. The free energy of activation, $\Delta G^{\ddagger}$ values were calculated from the formula of $\Delta G^{\ddagger} = \Delta H^{\ddagger} + T\Delta S^{\ddagger}$ at 150^{0}C. The entropy of activation ($\Delta S^{\ddagger}$) was calculated using the equation: $\Delta S^{\ddagger} = 4.576$ [log k_1-10.753-log T + ($\Delta H^{\ddagger}$ / 4.576T)]. Errors of the rate constants as well as enthalpy of activation ($\Delta H^{\ddagger}$) was calculated from

PSI plot at a 95% confidence limit. Error on the entropy of activation was calculated by taking a 5% of error on the activation energy.

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